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A Boxed Warning for Montelukast: The FDA Perspective

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Abbreviations: FDA = Food and Drug Administration, NP = neuropsychiatric, BW = boxed warning, AR = allergic rhinitis, EIB = exercise-induced bronchospasm, AC = advisory committee, ICS = inhaled corticosteroids, CysLT1 = cysteinyl leukotriene receptor 1, LTMA = leukotriene modifying agent

20 **Contributors' Statement Page**

21 Drs. Clarridge, Chin, Eworuke, and Seymour conceptualized the manuscript, drafted the initial
22 manuscript, contributed to revisions, and critically reviewed the final manuscript; and all authors
23 approved the final manuscript as submitted and agree to be accountable for all aspects of the
24 work.

25

Abstract

The FDA became aware of post-marketing reports of neuropsychiatric adverse events with Singulair (montelukast) use in 2007. Over the years, the Food and Drug Administration (FDA) has conducted reviews of the clinical trial safety data, focused analyses of post-marketing reports, and reviews of the published literature. These activities have resulted in successive labeling updates and public communications. However, there has been continued concern among stakeholders about the risk of neuropsychiatric events and the lack of awareness among prescribers and patients/caregivers. Based upon these concerns, FDA embarked on another comprehensive review and also conducted a new observational study using claims data in the Sentinel Distributed Database. In September 2019, FDA held a public Advisory Committee meeting to discuss its review and solicit recommendations from the panel regarding labeling and communication strategies. After careful consideration of the available data and feedback received during the FDA Advisory Committee meeting, the FDA required a boxed warning and a revision specifically for the allergic rhinitis indication to reserve use of montelukast to patients who have an inadequate response or intolerance to alternative therapies. Based upon benefit-risk considerations, the asthma indication was not changed. To provide insight into the process and rationale for the required labeling changes, we provide an overview of the decision-making framework we utilized.

Key words: boxed warning, montelukast, neuropsychiatric adverse events, leukotriene modifying agents, asthma, allergic rhinitis, exercise-induced bronchospasm

On March 4, 2020, the Food and Drug Administration (FDA) announced required labeling changes for montelukast (Singulair) to add a boxed warning (often called a “black box warning”) to strengthen the existing warning regarding the risk of neuropsychiatric (NP) events and a modified indication to limit use for allergic rhinitis, while maintaining that the benefit-risk decision regarding montelukast treatment in asthma should be evaluated on an individual basis.¹

Montelukast is a CysLT1 receptor antagonist, FDA-approved for the treatment of asthma, exercise-induced bronchospasm (EIB), and allergic rhinitis (AR). In 2007, FDA became aware of a new safety signal regarding NP events with montelukast use following Merck’s request to add depression and suicidal behavior to the label, and a reported suicide in a 15-year-old male taking montelukast. Review of the clinical trial safety database did not reveal a signal for neuropsychiatric events or suicidality for montelukast or other leukotriene modifiers. However, the clinical trials were short in duration and not designed to specifically examine neuropsychiatric events. The FDA reviewed post-marketing data in the FDA Adverse Event Reporting System (FAERS) Public Dashboard and identified a broad set of neuropsychiatric adverse event reports, some of which appeared consistent with a drug-induced effect but were typically non-serious and reversed with the cessation of therapy. Based upon the review of post-marketing adverse event reports, the FDA required a Precaution in the product labeling of montelukast to describe the variety of neuropsychiatric events reported. We also required similar changes in the labels of zafirlukast and zileuton because we could not rule out a potential class effect. The new safety information was subsequently conveyed through Drug Safety Communications and Dear Health Care Provider letters. Since then, additional NP event terms have been added to the montelukast label based on post-marketing reports. This safety issue with montelukast has also been discussed at FDA Advisory Committee (AC) meetings

(Nonprescription Drugs Advisory Committee Meeting, May 2014; Pediatric Advisory Committee Meeting, Sept 2014)^{2,3}, communicated through other forums, such as the American Academy of Pediatrics (AAP)⁴ and Medscape⁵, and continues to generate interest from patient and parent advocacy groups. The risk in pediatric patients has been of particular concern given the overlap in reported NP events and behavioral changes associated with normal development. Nonetheless, montelukast is widely prescribed for pediatric patients 0-16 years of age based on drug utilization data. The most common ICD-10 codes associated with dispensings are those for asthma, AR and cough (not necessarily with concomitant asthma), the latter of which suggests frequent off-label use in the youngest age groups.⁶

Over the past decade, FDA has continued to monitor and address reports of NP events associated with montelukast use. Recently, however, stakeholders raised concern that despite changes made to the montelukast labeling, it did not sufficiently characterize the risk, thereby prompting FDA to re-examine available data, including post-marketing reports, drug utilization, and recent literature. Because there were limited new data to evaluate this safety issue, FDA conducted an observational study using the Sentinel Distributed Database, a national medical product monitoring system based on a distributed data network of electronic healthcare and administrative claims data.⁷

Much of what the FDA knows about the nature of the NP safety signal has been through post-marketing reports, which have ranged from mild, reversible symptoms to rare, serious outcomes such as depression/suicide or persistent symptoms lasting well after treatment discontinuation. Published observational studies⁸⁻¹¹ have reported mixed results with some showing an association with montelukast use and NP events and others not. Further, the mechanism(s) by which montelukast may cause NP events remains unclear. Animal studies conducted by Merck

showed that montelukast can cross the blood-brain barrier in rats, but at low levels compared to other tissues. While several recent studies have suggested other potential mechanisms by which montelukast could gain access to the CNS, CysLT1 receptor expression in the human brain is very low, and hypothesized mechanisms such as antagonism of GPR17, a G-protein coupled receptor expressed on neurons and glial cells in the human brain, have been difficult to reproduce. Finally, the FDA-sponsored observational study did not provide further clarity as the results showed no association between depressive disorders, self-harm and suicides with montelukast (monotherapy) compared to inhaled corticosteroids (monotherapy). It is worth mentioning, however that despite the undeniable value of observational studies, outcomes are limited to those that resulted in healthcare claims, and thus cannot provide a clinical assessment of NP events nor its severity. In addition, only specific subsets of NP events including depression, self-harm and suicide are evaluable in these data sources. Lastly, due to confounding inherent to observational studies, a causal relationship between montelukast and NP events is difficult to establish the results of which were recently published.⁷

In September 2019, FDA convened a joint Pediatric AC and Drug Safety and Risk Management AC meeting to present and discuss FDA's review findings and seek input on changes to product labeling or other communications. The AC meeting generated public interest and included testimonies from patients and advocacy groups. Recurring themes voiced by the public and panel members included lack of awareness of the risk of NP events, the product label notwithstanding, and the perceived unfavorable benefit-risk for the AR indication. AC members acknowledged data limitations and lack of "new" information but noted the concerning nature of the post-marketing reports, particularly the descriptions of depression and suicidal ideation in pediatric patients. Patient and caregiver testimony during the meeting described the impact of

these events along with the frustration that healthcare providers did not discuss the risks of montelukast with them. Recommendations from the panel included revisions to product labeling, reevaluation of the benefit-risk for AR, additional research into the potential mechanism of action, and more education about the risk.¹²

Considering feedback from the AC meeting, FDA weighed the uncertainties surrounding the risk of NP events given the limitations of the available data with concerns raised by stakeholders along with our mission to uphold public health and regulatory standards. Our key priorities were to 1) increase awareness among patients and providers about the risk of NP events, especially when providers prescribe montelukast for off-label use where the benefit has not been established; 2) promote monitoring for these events by patients and providers; 3) maintain patient access to this drug for those whom the benefits outweigh the risks; 4) enhance scientific understanding about the risk; and 5) appropriately address stakeholder concerns. With these goals in mind, we assessed the regulatory tools available to us and developed a decision-making framework that weighed the benefits and risks of various regulatory actions for montelukast to determine the best method to achieve these goals. Examples of regulatory tools for this safety issue included labeling changes (e.g. addition of a BW), conducting or requiring additional studies, and issuing communications to the public. Given that the product label is the primary tool to communicate the safe and effective use of a product, labeling changes were a focus of our deliberations. When labeling adverse reactions in FDA-approved drug labeling (i.e., the Prescribing Information), FDA considers the evidence of a reasonable causal association, event frequency, and seriousness of events. Figure 1 describes key factors used in determining which safety section(s) of labeling are most appropriate for adverse reactions. Included in this assessment is the context of the benefits of the drug with respect to the condition it is intended to

138 treat. For example, the same adverse reaction may be labeled differently for a drug indicated for
139 a symptomatic, self-limited disease compared to a drug indicated for a serious and life-
140 threatening disease because the benefit-risk considerations are different.

141 A key decision was whether to elevate the risk of NP events to a Boxed Warning. During our
142 decision-making process, the FDA deliberated over a number of central issues: 1) the available
143 data regarding the risk of NP events, 2) the benefit-risk assessment for the asthma and AR
144 indications in the current therapeutic context, 3) the criteria for a BW, 4) the impact of a BW and
145 unintended consequences, and 5) the NP risk with other leukotriene inhibitors.

146 While there are limitations with the available data and uncertainties with respect to the frequency
147 of occurrence, the existing Warning/Precaution underscored our determination that there is a risk
148 of neuropsychiatric events with montelukast and some of these events are potentially serious.
149 However, we noted that the new available data did not provide additional clarity on the risk. Our
150 focus then turned to the benefit-risk assessment of montelukast, which was a recommendation
151 from the AC panel.

152 Within the decision-making framework, the FDA considered the benefit-risk assessment for each
153 individual indication for which montelukast is approved. AR is typically a mild, symptomatic
154 disease with a number of treatment options available by prescription and over-the-counter as
155 well as those that modulate the immune response to specific allergens (i.e., immunotherapy).
156 Treatment guidelines for AR recommend intranasal corticosteroids as first-line therapy with
157 addition of oral antihistamines for uncontrolled symptoms, both of which have extensive
158 histories of clinical use and safety.¹³ We considered the role of montelukast for the treatment of
159 AR and whether the potential risk of NP events outweighed the symptomatic benefit for patients

with AR. We concluded that the treatment landscape and benefit-risk assessment of montelukast for AR had changed since its initial approval. Given concerns related to NP events, the benefit-risk assessment was no longer favorable for montelukast use as the first treatment choice in patients with AR. The indication for montelukast has changed and its use should be reserved for patients with AR who have an inadequate response or intolerance to alternative therapies.

On the other hand, asthma is a heterogeneous disease with a variety of underlying etiologies, and thus symptoms and disease burden can vary widely in severity, and include significant morbidity, including hospitalization. There are a number of available therapies for asthma, including bronchodilators, inhaled corticosteroids, and injectable biologic products; however, these products do have risks to consider.¹⁴ Due to the potentially serious nature of asthma and spectrum of available therapies, we concluded that montelukast treatment should be evaluated on an individual basis such that the provider can make the appropriate benefit-risk decision regarding use of montelukast. A modification to the asthma indication was not warranted at this time.

Based upon the benefit-risk considerations described above, we determined that the risk of NP events should be elevated to a BW because it met the criteria of being serious in proportion to the potential benefit and is essential to be considered in assessing whether to prescribe the drug. This decision was driven by the change in benefit-risk assessment for AR.

The next consideration was the impact of the regulatory action (addition of a BW, modified AR indication) and potential unintended consequences. We considered that a BW is used to call attention to safety concerns with products and would align with the goal of raising awareness for prescribers and that previous labeling changes have not effectively communicated the risk of NP events. An unintended consequence of a BW is that it could lead to discontinuation of the

product by the patient. We would recommend patients discuss any change in medication with their healthcare provider. We anticipate this discussion about benefits and risks of montelukast to be a positive outcome of the BW. Overall, these labeling changes may lead to decreased prescribing of montelukast for AR in patients in whom the benefits do not outweigh the risks. We intend to monitor the utilization over time to determine the impact on prescribing.

Finally, the FDA further considered whether revisions to the zafirlukast and zileuton product labeling might be warranted. In 2009, FDA required a Precaution on the zafirlukast and zileuton product labels regarding the risk of NP events. We now had to consider whether these products should also have a BW. As noted in the FAERS review, there have been few post-marketing reports of NP events with zafirlukast and zileuton. But, compared to montelukast, zafirlukast and zileuton are used infrequently; therefore, the paucity of post-marketing NP reports with these products is not unexpected and the absence of a clear post-marketing safety signal with the other two leukotriene modifying agents (LTMA) products may simply be a reflection of low drug utilization. A structural analysis of the LTMA products performed by the FDA Division of Applied Regulatory Sciences revealed that montelukast is structurally dissimilar and does not share many chemical features with either zafirlukast, a leukotriene receptor blocker, or zileuton, an inhibitor of 5-lipoxygenase. Additionally, neither zafirlukast nor zileuton possess the quinoline substructure contained within montelukast, which has been described in other drug classes that are associated with NP adverse events via the tryptophan/kynurenine pathway. While montelukast has the potential to bind many different off-target receptors in the CNS, including proteins known to produce NP events, neither zafirlukast or zileuton are predicted to act at these receptors within the CNS. Therefore, mechanistically, there is little reason to expect or predict direct CNS effects from either zafirlukast and zileuton. Furthermore, neither zafirlukast and

zileuton are approved for AR, the indication for which the benefit-risk assessment has substantially changed in light of the risk of NP events and landscape of available alternative therapies. Based on these factors, the FDA did not require a BW or further labeling changes to the zafirlukast and zileuton labels.

The FDA acknowledges the limitations of the data surrounding the risk of NP events, given that the signal is based upon post-marketing reports, which are voluntary and often limited in detail. Incidence rates are inherently difficult to calculate using post-marketing data as we do not know the total number of events occurring in the population or the total number of exposures. Reports are influenced by additional factors, including the severity of the case, the amount of time the medication has been on the market, media exposure regarding adverse events for the medication in question, and the background rate of the adverse event for the population in question. The lack of clear understanding of the potential cause or mechanism of action further adds to the ambiguity. Nonetheless, the FDA concluded that requiring a BW and limiting the AR indication for montelukast was warranted based upon an unfavorable benefit-risk assessment for montelukast when used to treat mild disease such as AR given the modest treatment benefit, potential severity of NP events, and wide availability of convenient alternative treatment options with well-established safety and efficacy profiles. Communicating this potential safety risk to a broad audience is of utmost importance given the widespread labeled and off-label use in pediatric patients and the myriad reported NP events that overlap with normal developmental changes.

227 *Figure 1. Key Regulatory Factors Used In Determining Which Safety Section(s) of Labeling Are Most Appropriate For Adverse*
228 *Reactions*

229 ¹For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with
230 use of a drug for which there is some basis to believe there is a causal relationship between the drug and the
231 occurrence of the adverse event.

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ADVERSE REACTIONS ¹	WARNINGS AND PRECAUTIONS	CONTRAINDICATIONS	BOXED WARNING
•Describes the overall adverse reaction profile of the drug based on the entire safety database (clinical trials and post-marketing) •Generally does not include adverse events that are infrequent and minor or those not plausibly related to drug therapy	•Describes clinically significant adverse reactions including: ○ Potentially fatal reactions ○ Serious reactions, even if infrequent ○ Reactions that can be prevented or mitigated through appropriate use of the drug	•Describes any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. •Only includes known hazards, and not theoretical possibilities	•Describes certain contraindications or serious warnings, particularly those that may lead to death or serious injury •Used to highlight certain situations including: ○ Adverse reactions so serious in proportion to the potential benefit it is essential to be considered in assessing whether to prescribe the drug ○ Serious adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug