Testimony Before the FDA's Pediatric Advisory Committee and Drug Safety and Risk Management Advisory Committee - Neuropsychiatric Events with Use of Montelukast in Pediatric Patients

September 27, 2019

Meena M. Aladdin, Ph.D.
Health Researcher, Public Citizen's Health Research Group

I have no financial conflicts of interests.

Major Comment

- This is the second advisory committee meeting convened to discuss the labeling of montelukast and the risk of neuropsychiatric adverse events. On September 23, 2014, the Pediatric Advisory Committee unanimously made the following recommendations:
  - Formatting the label to highlight the potential for adverse events.
  - Improve communication with healthcare providers so that they informed them of label changes to better counsel their patients about risks with montelukast.
- The FDA then corresponded with the sponsor to consider communication options to healthcare providers such as Dear Health Care Provider letters and Drug Safety Communications, but it was felt that these communications were not warranted.
- The FDA did collaborate with Medscape, to communicate the effects of leukotriene modifiers to healthcare providers, but this effort was insufficient as there is evidence to suggest that caregivers were not adequately communicating the risks associated with this drug.

We strongly urge the committees to recommend that the FDA strengthen warnings on product labeling and improve caregiver communication to mitigate the potential risks of neuropsychiatric events associated with Montelukast use.

Ongoing Risk Communication Problems

- The FDA noted in its briefing document:
  - "Despite FDA's communication efforts and information in the product label, stakeholders have raised concerns that many physicians and patients are not aware of the risk for neuropsychiatric events nor what to do if symptoms occur."
  - "Interestingly, despite the majority of cases being reported by family members and consumers, we noted that no cases confirmed receiving patient counseling regarding possible neuropsychiatric effects of montelukast. Most cases [reported to FAERS] did not report any information regarding the presence or absence of patient counseling, but six confirmed that they did not receive healthcare provider counseling."

Prevalent use of Montelukast and Asthma Rates

- Compounding the issue of a lack of effective care provider communication, is the widespread use of montelukast, particularly among pediatric patients.
  - An estimated total of 2.3 million pediatric patients 0-16 years old (a quarter of the total 9.3 million patients of all ages) were dispensed montelukast in 2018.

Montelukast Exposure and Biological Potential for Off-Target Effects

- Montelukast binds to the cysteinyl leukotriene receptor-1 (CYSLTR1) to prevent the interaction of this receptor with the inflammatory mediators, leukotrienes.
- Expression of this receptor is not limited to the lung; there is a growing body of evidence to show that this it is expressed in different cells in the brain, including microvascular endothelial cells-components of the blood brain barrier (Marshallinger J, et al, *Nat Commun,* 2015*;* Zhang WP, et al. *Neurosci Lett,* 2004; Lenz QF, et al, *Neuroscience,* 2014)
- Animal studies have amply demonstrated that montelukast administered orally can be found in the brain (Zhao et al, *J Pharm Pharmacol*, 2011; Zhang CT, et al, *Neurotoxicology,* 2016).
  - “The biologic mechanisms underlying the neuropsychiatric events associated with montelukast treatment are currently not well understood. However, evidence from animal studies suggests that montelukast could act directly on cells in the brain. Orally administered montelukast (10 mg/kg/day, 7 days) was detectable in brain tissue and cerebrospinal fluid (CSF) in rats9, providing evidence for its ability to cross the blood-brain barrier” (FDA briefing document).

Other Factors to Support Stronger Warnings

- **Precautionary Principle:** In the presence of gaps in knowledge, it is safer to err on the side of caution and take necessary steps to protect patients.
- Enhanced warnings, such as boxed warnings do not require the establishment of a causal relationship between a drug and adverse events (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf).
- Confirmed cases of positive de-challenge and re-challenge and the reemergence of neuropsychiatric symptoms
  - Two cases described symptom resolution following montelukast reinitiation (positive dechallenge)(FDA briefing document)

Conclusions

- We hereby urge the committees to recommend that the FDA require:
  - Addition of a black-box warning to the product labeling for montelukast about the potential for neuropsychiatric adverse events.
  - Distribution of letters to healthcare providers/prescribers to better counsel them on montelukast use, the risk of neuropsychiatric events, and the importance of counseling patients to monitor for these events.
  - An FDA-approved medication guide containing prominent warnings about neuropsychiatric adverse events that is provided to patients or their caregivers when montelukast is dispensed.

Given the lack of communication between prescribers and patients and gaps in knowledge regarding montelukast's effects in brain, we strongly urge the committee recommend to FDA to take action and strengthen warnings associated with montelukast use.

Bibliography

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