FDA Joint Meeting of the Pediatric and Drug Safety and Risk Management Advisory Committees

Neuropsychiatric Events with the use of Montelukast in Pediatric Patients

Katherine Clarridge, MD, MSc
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
September 27, 2019
Objectives

• Discuss ongoing concerns regarding neuropsychiatric adverse events with montelukast, particularly in pediatric patients

• Present FDA’s review of available data and regulatory considerations

• Obtain input and recommendations from the Advisory Committees
FDA Agenda

• Background
• Pediatric Utilization Patterns
• Postmarketing Pharmacovigilance Review
• Risk of Neuropsychiatric Adverse Events
  – Literature
  – Sentinel
• Summary
FDA Presentation Outline

• Product Information
• Regulatory History Related to Neuropsychiatric Findings
• Current Review of Montelukast and Neuropsychiatric Events
• Regulatory Considerations
• Discussion Topics
Product Information

• Montelukast (Singulair)
• Mechanism of Action: specific cysteinyl leukotriene type-1 receptor antagonist (CYSLT-1)
• Approved for:
  – prophylaxis and chronic treatment of asthma
  – seasonal or perennial allergic rhinitis
  – prevention of exercise-induced bronchoconstriction
• Multiple abbreviated new drug applications (ANDAs)
Approval History

- Tablets 10 mg: approved February 1998
- Tablets 4 mg, 5 mg: approved February 1998
- Chewable Oral Granules 4 mg: approved July 2002

<table>
<thead>
<tr>
<th>Indication/Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>10 mg</td>
</tr>
<tr>
<td>6-14 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>12 months - 5 years</td>
<td>4 mg</td>
</tr>
<tr>
<td><strong>Seasonal Allergic Rhinitis (SAR)</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>10 mg</td>
</tr>
<tr>
<td>6-14 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>2-5 years</td>
<td>4 mg</td>
</tr>
<tr>
<td><strong>Perennial Allergic Rhinitis (PAR)</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>10 mg</td>
</tr>
<tr>
<td>6-14 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>6 months - 5 years</td>
<td>4 mg</td>
</tr>
<tr>
<td><strong>Exercise-Induced Bronchoconstriction (EIB)</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>10 mg</td>
</tr>
<tr>
<td>6-14 years of age</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Source: Singulair Prescription Package Insert
FDA Presentation Outline

• Product Information
• Regulatory History Related to Neuropsychiatric Findings
• Current Review of Montelukast and Neuropsychiatric Events
• Regulatory Considerations
• Discussion Topics
Regulatory History Related to Neuropsychiatric Adverse Events
“Tremor”, “Depression”, and “Suicidal thinking and behavior”

Letter received from New York Senator

Regulatory History
Regulatory History

- FDA posted Early Communication
- “Tremor”, “Depression”, and “Suicidal thinking and behavior”
- Letter received from New York Senator
- 2007 to 2019 timeline with specific years highlighted.
“Tremor”, “Depression”, and “Suicidal thinking and behavior”

FDA posted Early Communication

Addition of Neuropsychiatric Adverse Events to Warnings and Precautions

Letter received from New York Senator

FDA updated Early Communication in January and August

Merck and AstraZeneca send DHCP letters

2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019

Regulatory History
Regulatory History

- FDA posted Early Communication
- "Tremor", "Depression", and "Suicidal thinking and behavior"
- Citizen’s Petition from Parent’s group
- 2007 Letter received from New York Senator
- FDA updated Early Communication in January and August
- 2008 FDA posted Early Communication
- 2009 Addition of Neuropsychiatric Adverse Events to Warnings and Precautions
- 2010 Merck and AstraZeneca send DHCP letters
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
Regulatory History

- 2007: Letter received from New York Senator
- 2008: FDA updated Early Communication in January and August
- 2009: FDA posted Early Communication
- 2010: “Tremor”, “Depression”, and “Suicidal thinking and behavior”
- 2011: Citizen’s Petition from Parent’s group
- 2012: Nonprescription Drugs Advisory Committee (NDAC)
- 2013: Addition of Neuropsychiatric Adverse Events to Warnings and Precautions
- 2014: Pediatric Advisory Committee (PAC)
- 2015:
- 2016:
- 2017:
- 2018:
- 2019:
- Merck and AstraZeneca send DHCP letters
“Tremor”, “Depression”, and “Suicidal thinking and behavior”

2007:
- Letter received from New York Senator

2008:
- FDA posted Early Communication
- “Tremor”, “Depression”, and “Suicidal thinking and behavior”

2009:
- Citizen’s Petition from Parent’s group
- FDA updated Early Communication in January and August

2010:
- Merck and AstraZeneca send DHCP letters
- Nonprescription Drugs Advisory Committee (NDAC)

2011:
- FDA conducts interview with Medscape
- FDA posted Early Communication

2012:
- Pediatric Advisory Committee (PAC)

2013:
- American Academy of Pediatrics (AAP) published FDA Update

2014:
- Addition of Neuropsychiatric Adverse Events to Warnings and Precautions

2015:
- Nonprescription Drugs Advisory Committee (NDAC)

2016:
- FDA conducts interview with Medscape

2017:

2018:

2019:
Addition of Neuropsychiatric Adverse Events to Warnings and Precautions

“Tremor”, “Depression”, and “Suicidal thinking and behavior”

“Hostility” and “Somnambulism”

“Disorientation”

“Tic”

“Dysphemia”

“Obsessive-compulsive symptoms”
5.4 Neuropsychiatric Events
Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Postmarketing reports with SINGULAIR use include, but are not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some postmarketing reports involving SINGULAIR appear consistent with a drug-induced effect. Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur [see Adverse Reactions (6.2)].
Montelukast Patient Information

What are the possible side effects of SINGULAIR?

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - attention problems
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability

- **Other side effects**:
  - memory problems
  - obsessive-compulsive symptoms
  - restlessness
  - sleep walking
  - stuttering
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping
  - uncontrolled muscle movements
FDA Presentation Outline

• Product Information
• Regulatory History Related to Neuropsychiatric Findings
• Current Review of Montelukast and Neuropsychiatric Events
• Regulatory Considerations
• Discussion Topics
The letter requested the following from the FDA:

1) Determine the mechanisms for montelukast’s neuropsychiatric side effects
2) Determine the risk factors for neuropsychiatric adverse reactions
3) Determine the appropriate way to discontinue montelukast
4) Evaluate withdrawal symptoms and long-term sequelae of an adverse reaction
5) Reclassify neuropsychiatric side effects of montelukast to be common in children
6) Update labeling to include a warning for “excoriation”, “hyperkinesia”, and “obsessive-compulsive disorder”
7) Issue a Medication Guide for montelukast
8) Consider a boxed warning
FDA Review

- Reviewed postmarketing pharmacovigilance data (FAERS)
- Reviewed observational literature
- Designed and conducted study in Sentinel
- Evaluated pediatric utilization patterns
- Reviewed nonclinical (animal) studies
- Explored communication strategies
FDA Presentation Outline

• Product Information
• Regulatory History Related to Neuropsychiatric Findings
• Current Review of Montelukast and Neuropsychiatric Events
• Regulatory Considerations
• Discussion Topics
Labeling - Warnings and Precautions

• Product labeling conveys essential information for safe and effective use

• Neuropsychiatric Events are listed in the Warnings and Precautions section (5.4) of the label
Medication Guide

• FDA required patient labeling
• 21 CFR 208.1
  – Patient labeling could help prevent serious adverse effects
  – Serious risks (relative to benefits) of which patients should be made aware because information could affect decision to use the product
  – Patient adherence instructions for use is crucial to drug’s effectiveness
Boxed Warning

• Used to call attention to serious or life-threatening risks

• 21 CFR 201.57(c)(1)
  – Adverse reaction so serious in proportion to benefit that it is essential to consider in assessing risks and benefits of using the drug
  – Serious adverse reaction that can be prevented or reduced by appropriate use
  – Approved with restrictions to ensure safe use because drug can be safely used only if distribution or use is restricted
FDA Presentation Outline

• Product Information
• Regulatory History Related to Neuropsychiatric Findings
• Current Review of Montelukast and Neuropsychiatric Events
• Regulatory Considerations
• Discussion Topics
Discussion Topics

1) Neuropsychiatric safety findings presented for montelukast
2) Labeling for montelukast, including
   • Current Warnings and Precautions
   • Request for Medication Guide and Boxed Warning
3) Recommendations for communication strategies
   • Target audience
   • Target organizations
   • Modalities of communication