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Testimony Before the FDA's Nonprescription Drugs Advisory Committee
Regarding New Drug Application 204804 for Montelukast (Singulair Allergy)

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group, testifying on behalf of myself and Dr. Sidney Wolfe, the founder of our group. We have no financial conflicts of interest.

We strongly oppose Food and Drug Administration (FDA) approval of over-the-counter (OTC) montelukast because, relative to existing FDA-approved OTC products for allergic rhinitis, the drug:

(1) offers marginal clinical benefit relative to placebo and generally appears to have inferior effectiveness compared to existing FDA-approved OTC allergy products; and
(2) poses significantly greater risk, both to patients who meet the proposed indication and to those likely to use the drug for off-label indications.

Efficacy Assessment: Marginal Benefit

Table 1 demonstrates that montelukast is no better, and perhaps worse, than loratadine for treating seasonal allergic rhinitis (SAR).[1] Compared to placebo, it showed marginal benefit in phase 2 and 3 studies, with the mean change from baseline daytime nasal symptom scores ranging from -0.06 to -0.23 (on a scale ranging from 0 to 3).

Table 1: Premarketing Efficacy Results in SAR Clinical Studies

Study	Daytime Nasal Symptom Score (Mean Change from Baseline)				
	Montelukast 10mg	Loratadine 10mg	Placebo	Montelukast vs. Placebo	
				Effect Size	p value
Phase 3 Studies					
117	-0.47 (N=151)	-0.51 (N=300)	-0.22 (N=148)	-0.23	≤0.001
162†	-0.39 (N=344)	-0.46 (N=599)	-0.26 (N=351)	-0.13	≤0.001
192†	-0.38 (N=326)	-0.45 (N=168)	-0.30 (N=331)	-0.06	0.10
235†	-0.39 (N=519)	-0.50 (N=170)	-0.31 (N=521)	-0.09	0.003
240	-0.32 (N=445)	-0.45 (N=180)	-0.20 (N=448)	-0.10	0.003
Phase 2 Studies					
68	-0.34 (N=94)	-0.32 (N=91)	-0.24 (N=89)	-0.11	0.149
77	-0.31 (N=111)	-0.42 (N=115)	-0.12 (N=57)	-0.18	0.027
102	-0.32 (N=103)	-0.27 (N=162)	-0.25 (N=53)	-0.07	0.383

† Resubmitted for evaluation of ocular symptom indication

Source: Clinical review by Dr. Erika Torjusen (DPARP)

Study 117 Clinical Study Report p17, Study 162 Clinical Study Report p18, Study 192 Clinical Study Report p17, Study 235 Clinical Study Report p17, Study 240 Clinical Study Report p20, Study 68 Clinical Study Report p15, Study 77 Clinical Study Report p15, Study 102 Clinical Study Report p17.

[1] Food and Drug Administration. FDA briefing document: Nonprescription Drugs Advisory Committee Meeting Montelukast (Singulair Allergy). May 2, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM395173.pdf. PDF page 10. Accessed April 30, 2014.

One study in perennial allergic rhinitis (PAR) patients (study 246) revealed that montelukast was no better than placebo, whereas cetirizine was statistically better in improving daytime nasal symptom scores. A second study (study 265) showed that montelukast had a greater effect than placebo, but the difference (-0.08) was not clinically meaningful.

Table 4: Premarketing Efficacy Results in PAR Clinical Studies: Study 246

Treatment Groups	N	Mean Baseline DNSS Score	Mean Change from Baseline in DNSS	LS mean Treatment vs. Placebo (p value)
Primary Efficacy Endpoint – DNSS				
Montelukast 10mg	626	2.08	-0.39	-0.04 (0.150)
Cetirizine 10mg	120	2.13	-0.47	-0.10 (0.038)
Placebo	609	2.07	-0.35	--

DNSS: Daytime Nasal Symptom Score
Source: Study 246 Clinical Study Report p21, p95.

Table 5: Premarketing Efficacy Results in PAR Clinical Studies: Study 265

Treatment Groups	N	Mean Baseline DNSS Score	Mean Change from Baseline in DNSS	LS mean Treatment vs. Placebo (p value)
Primary Efficacy Endpoint – DNSS*				
Montelukast 10mg	1000	2.09	-0.42	-0.08 (≤0.001)
Placebo	980	2.10	-0.35	--

Source: Study 265 Clinical Study Report p15, p67.
DNSS: Daytime Nasal Symptom Score; *Nasal itching not included in score.

In assessing the efficacy of montelukast, reviewers in FDA's Division of Pulmonary, Allergy, and Rheumatology Products noted:[2]

> A number of practice parameters and guidelines, which are largely in agreement with each other, have been set forth to aid in the treatment of patients. Intranasal corticosteroids are recommended as first-line therapy for moderate- to-severe allergic rhinitis, with second-generation oral antihistamines generally preferred for the treatment of mild allergic rhinitis owing to their safety and ease of use. Intranasal corticosteroids can be combined with second-generation oral antihistamines for persistent symptoms. …
>
> Thus, per clinical guidelines, montelukast's role is generally as an adjunct in the treatment of a patient who does not have an adequate response to an antihistamine, a nasal corticosteroid, or both. **However, there are no clear data demonstrating that leukotriene-receptor antagonists combined with either antihistamines or nasal corticosteroids reduce symptom scores more than antihistamines or corticosteroids alone.** [Emphasis added]

[2] *Ibid*. PDF pages 22-23.

Risk of Serious Harm

Neuropsychiatric Harms

Montelukast poses many serious risks that are unique compared to other OTC drugs for allergic rhinitis. Among the most concerning are the neuropsychiatric adverse events. Pharmacovigilance data presented to the FDA and numerous reports in the medical literature demonstrate associations with montelukast exposure and the following in adults, adolescents, and pediatric patients:[3]

- agitation
- aggressive behavior or hostility
- anxiousness
- depression
- disorientation
- disturbance in attention
- dream abnormalities, including nightmares
- hallucinations
- insomnia
- irritability
- memory impairment
- restlessness
- somnambulism
- suicidal thinking and behavior (including suicide)
- tremor

The current drug label for prescription montelukast discusses this association in the WARNINGS AND PRECAUTIONS section:[4]

> **The clinical details of some post-marketing 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.** [Emphasis added]

Many reports of neuropsychiatric adverse events associated with montelukast exposure provide compelling evidence of a causal link to the drug. For example:

- Cereza, et al. (2012) reported data gathered from 24 reports of nightmares in 17 children and seven adults treated with montelukast.[5] Fourteen had concomitant psychiatric symptoms: insomnia (n=5), nervousness (n=4), hallucinations (n=3), aggressiveness (n=2), irritability (n=2), and anxiety (n=1).

[3] *Ibid*. PDF pages 32, 56.
[4] Merck Sharp & Dohme. Drug label for Singulair (montelukast sodium) tablets, chewable tablets, and oral granules. Revised December 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021409s043lbl.pdf. Accessed April 30, 2014.
[5] Cereza G, Dolade NG, Laporte J-R. Nightmares induced by montelukast in children and adults. *Eur Resp J*. 2012;40(6):1574-1575

> In all cases, montelukast was the only suspect drug. In 18 patients, the nightmare appeared within the first day (n=11) or first week (n=7) of exposure. Nightmares rapidly resolved with discontinuation of montelukast in 21 cases. Three patients were re-exposed to the drug after nightmares had resolved, and in all three nightmares recurred.

- Bygdell, et al. (2012) presented data on spontaneous reports of psychiatric adverse events in children in the Swedish Drug Information System for 2001-2010.[6] Of 744 such events, montelukast was the most frequently suspected drug after exclusion of vaccines, involving 92 cases. The most common reactions were nightmares (n=19), aggressiveness (n=13), sleep disorder (n=11), personality disorder (n=9), anxiety (n=9), and hyperactivity (n=8). Ninety-three percent had a positive dechallenge; 38 percent had a positive rechallenge.
- The FDA highlighted "ten sample suicide case reports for which the behavior change appears to be correlated with use of the drug or the suicide occurs within a short time after starting or restarting montelukast."[7]

High Likelihood of Inappropriate, Potentially Dangerous Off-Label Use

The potential for inappropriate and potentially dangerous off-label use of OTC montelukast by adolescents and children and by patients with asthma is high for several reasons. First, the potential target population for use of OTC montelukast is huge, with allergic rhinitis affecting as many as 30-60 million people in the U.S., including 10-30 percent of adults and up to 40 percent of children.[8] Second, there is considerable overlap between allergic rhinitis and asthma, with 10-40 percent of patients with allergic rhinitis having coexisting asthma, and up to 90 percent of asthmatics having concomitant allergic rhinitis.[9] Third, the consumer studies indicated, among other things, that many consumers, particularly those with low literacy and adolescents, misunderstood for whom the drug is intended.[10] Fourth, if approved, this would be the only available OTC product that is also approved by the FDA in prescription form for asthma treatment. Combining these factors with the expected wave of aggressive direct-to-consumer advertising by Merck will undoubtedly lead to off-label use by many patients, including asthmatics.

The FDA highlighted the danger posed by such off-label uses when it noted:[11]

> One potential concern regarding montelukast use in the OTC setting is that consumers may assume montelukast is effective for acute asthma attacks and delay effective treatment. Some examples from [Merck's pharmacovigilance database] follow patients on montelukast for a short time, where **there appears to be a delay in effective treatment for acute asthma attacks—with fatal outcome**. [Emphasis added]

[6] Bygdell M, Brunlöf G, Wallerstedt S, and Kindblom J. Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. *Pharmacoep Drug Saf.* 2012; 21(1):79–86.
[7] Food and Drug Administration. FDA briefing document: Nonprescription Drugs Advisory Committee Meeting Montelukast (Singulair Allergy). May 2, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM395173.pdf. PDF pages 63-64. Accessed April 30, 2014.
[8] *Ibid*. PDF pages 6-7.
[9] *Ibid*. PDF page 7.
[10] *Ibid*. PDF pages 134-167.
[11] *Ibid*. PDF page 54.

Other Risks

- Systemic eosinophilia, with features of vasculitis consistent with Churg-Strauss syndrome.[12]
- Hepatic injury[13]
- Angioedema and allergic reactions[14]
- Potential, dangerous interaction with grapefruit juice[15]

Conclusions

No other country has approved OTC montelukast, and the FDA should not make the mistake of having the U.S. be the first to do so. We urge the committee to recommend against FDA approval of OTC montelukast for allergic rhinitis because:

- There is no evidence that the drug is more effective than, or even as effective as, the existing FDA-approved OTC allergy drugs;
- there is no evidence that it provides any additional benefit when combined with these other drugs; and
- its risk profile is clearly worse than existing OTC treatments for allergic rhinitis.

[12] Merck Sharp & Dohme. Drug label for Singulair (montelukast sodium) tablets, chewable tablets, and oral granules. Revised December 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021409s043lbl.pdf. Accessed April 30, 2014.
[13] *Ibid*.
[14] *Ibid*.
[15] Cingi C, Toros SZ, Gurbuz MK, et al. Effect of grapefruit juice on bioavailability of montelukast. *Laryngoscope*. 2013;123:816-819.