Testimony Before the FDA's Nonprescription Drugs Advisory Committee Regarding Montelukast (Singulair Allergy): Risks Outweigh Benefits

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(We have no financial conflicts of interest)

Introduction: Oppose Approval

- We strongly oppose FDA approval of OTC montelukast because, relative to existing FDA-approved OTC products for allergic rhinitis, the drug:
  - offers marginal clinical benefit relative to placebo and generally appears to have inferior effectiveness compared to existing FDA-approved OTC allergy products; and
  - poses significantly greater risk, both to patients who meet the proposed indication and to those likely to use the drug for off-label indications.

Marginal Benefits: Seasonal Allergic Rhinitis

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. Er ka 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.

Marginal Benefits: Perennial Allergic Rhinitis

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.				

FDA Reviewers Assessment of Efficacy

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.

Risk of Serious Harm: Neuropsychiatric

- 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

Prescription Montelukast Drug Label Warnings and Precautions

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.

Evidence of a Causal Link Between Neuropsychiatric Events and Montelukast

- Cereza, et al. (2012) reported data gathered from 24 reports of nightmares in 17 children and 7 adults using montelukast.
- 14 had concomitant psychiatric symptoms.
- 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) or 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.

Evidence of a Causal Link Between Neuropsychiatric Events and Montelukast

- Bygdell, et al. (2012) presented data on spontaneous reports of psychiatric adverse event in children in the Swedish Drug Information System for 2001-2010.
- 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.

High Likelihood of Inappropriate, Potentially Dangerous Off-Label Use

- Huge potential target population (30-60 million allergic rhinitis (AR) patients in the U.S)
- Considerable overlap between AR and asthma (10-40% of AR patients have asthma; 90% of asthma patients have AR)
- Consumer studies indicated that many consumers, particularly those with low literacy and adolescents misunderstood for whom the drug is intended.
- If approved, it would be the only available OTC product that is also approved by the FDA in prescription form for asthma treatment
- Aggressive direct-to-consumer advertising

Other Risks

- Systemic eosinophilia, with features of vasculitis consistent with Churg-Strauss syndrome.
- Hepatic injury
- Angioedema and allergic reactions
- Potential dangerous interaction with grapefruit juice (Cingi C et al. *Laryngoscope*. 2013;123:816-819

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.