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Dear Drs. Ostroff, Woodcock, and Yim:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) not to approve the new drug application (NDA) 207988 for lesinurad submitted by Ardea Biosciences, Inc, for the proposed indication of treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor. Lesinurad was the subject of the October 23, 2015, Arthritis Advisory Committee (AAC) meeting, and the Prescription Drug User Fee Act target goal date for FDA action on lesinurad is December 29, 2015.[1] This letter supplements Public Citizen's testimony presented at that meeting.

We strongly oppose FDA approval of lesinurad for the proposed indication because:

[1] AstraZeneca. FDA advisory committee recommends the approval of lesinurad for gout patients. October 23, 2015. https://www.astrazeneca.com/our-company/media-centre/press-releases/2015/-fda-advisory-committee-recommends-the-approval-of-lesinurad-for-gout-patients-23102015.html. Accessed December 3, 2015.

(1) The drug offers meager clinically meaningful benefits relative to placebo for gout patients with hyperuricemia;
(2) The drug has serious risks, including definite significant renal toxicity and possible cardiovascular toxicity; and
(3) As a result, the risks of the drug far outweigh its benefits.

Indeed, at the AAC meeting on October 23, there was recognition by some AAC members and by the FDA's Dr. Yim that the therapeutic index for lesinurad is unacceptably narrow, with the minimum effective dose being essentially the same as the maximum safe dose. Approval of such a drug would be inconsistent with the precautionary principle for protecting public health.

Efficacy Assessment: Meager Clinical Benefit

The sponsor's NDA submission for lesinurad included data from three randomized, double-blind, placebo-controlled phase 3 trials. The trials evaluated the urate-lowering effect of 200 milligram (mg) or 400 mg doses of lesinurad versus placebo once daily combined with a xanthine oxidase inhibitor (allopurinol [studies 301 and 302] or febuxostat [study 304]) for 12 months.[2] The sponsor is seeking approval for only the 200 mg dose.

In studies 301 and 302, the proportion of subjects who achieved the primary endpoint (a serum uric acid level <6 mg/dl by month 6) was higher in both the 200 mg and 400 mg lesinurad groups compared with the placebo group.[3] The differences were statistically significant for both lesinurad doses in both trials.

The results from study 304 were less robust: The proportion of subjects who achieved the primary endpoint (a serum uric acid level <5 mg/dl by month 6) was higher in both the 200 mg and 400 mg lesinurad groups in a dose-dependent manner compared with the placebo group.[4] This difference was statistically significant only for the 400 mg lesinurad group. However, statistically significant differences in the proportions of subjects treated with 200 mg lesinurad who achieved a serum uric acid <5 mg/dL were observed at the month 5, month 8, and later time points as compared with the placebo-treated subjects.[5]

The FDA reviewers emphasized that the magnitude of lesinurad's urate-lowering effect was only modest for all three trials. For studies 301 and 302, the adjusted difference in mean serum uric acid change over baseline for the lesinurad 200 mg treatment groups versus the placebo groups ranged from 1.01-1.09 mg/dL at month 6 to 0.89-0.93 mg/dL at month 12.[6] Likewise, in study 304, the adjusted difference in mean serum uric acid change over baseline for the lesinurad 200 mg

[2] Food and Drug Administration. Briefing document for the October 23, 2015, meeting of the Arthritis Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM467942.pdf. Accessed December 1, 2015. PDF page 61.
[3] *Ibid*. PDF pages 9-10.
[4] *Ibid*. PDF pages 10-11.
[5] *Ibid*. PDF page 62.
[6] *Ibid*. PDF page 61.

treatment group versus the placebo group ranged from 0.79 mg/dL at month 6 to 1.06 mg/dL at month 12.[7]

More importantly, the FDA reviewers noted that the changes in the surrogate endpoint were not associated with any statistically significant differences favoring the 200 mg lesinurad-treated subjects on clinically meaningful secondary endpoints in any of the three pivotal clinical trials, including rate of gout flares requiring treatment in months 6 to 12, resolution of tophi by month 12, and measures of patient disability (see tables 1-3 below).[8]

Table 1: Study 301, Key Secondary Endpoint Results

	Placebo + ALLO (N=201)	**Lesinurad 200mg + ALLO (N=201)**	**Lesinurad 400mg + ALLO (N=201)**
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	0.58 (0.10)	0.57 (0.10)	0.51 (0.09)
Incidence rate ratio vs. placebo + ALLO (95% CI) p-value		0.99 (0.61, 1.61) p=0.98	0.88 (0.54, 1.43) p=0.61
Of patients with ≥1 tophus at baseline, proportion with target tophus resolution at 12 months	5/17 (29%)	0/18 (0%)	4/19 (21%)
Difference vs. placebo + ALLO (95% CI), p-value		-0.29 (-0.51, -0.08) p=0.02	-0.08 (-0.37, 0.20) p=0.60

Abbreviations: ALLO, allopurinol; CI, confidence interval

[7] *Ibid*. PDF page 62.
[8] *Ibid*. PDF pages 78, 79. 80, 83. (See also Errata at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM467946.pdf. PDF page 1).

Table 2: Study 302, Key Secondary Endpoint Results

	Placebo + ALLO (N=206)	Lesinurad 200mg + ALLO (N=204)	Lesinurad 400mg + ALLO (N=200)
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	0.83 (0.13)	0.73 (0.12)	0.77 (0.13)
Incidence rate ratio vs. placebo + ALLO (95% CI) p-value		0.88 (0.57, 1.37) p=0.57	0.93 (0.60, 1.45) p=0.75
Of patients with ≥1 tophus at baseline, proportion with target tophus resolution at 12 months	11/33 (33%)	11/35 (31%)	8/29 (28%)
Difference vs. placebo + ALLO (95% CI), p-value		-0.02 (-0.24, 0.20) p=0.85	-0.06 (-0.29, 0.17) p=0.63

Abbreviations: ALLO, allopurinol; CI, confidence interval

Table 3: Study 304, Select Key and Other Secondary Endpoint Results

	Placebo + FBX (N=109)	Lesinurad 200mg + FBX (N=106)	Lesinurad 400mg + FBX (N=109)
Mean adjusted rate of gout flares requiring treatment per subject in months 6-12 (standard error)	1.3 (0.25)	1.5 (0.31)	0.7 (0.15)
Incidence rate ratio vs. placebo + FBX (95% CI), p-value		1.2 (0.7, 2.1) p=0.55	0.5 (0.3, 1.0) p=0.04
Proportion with a CR or PR of at least one target tophus by month 12	55 (51%)	60 (57%)	64 (59%)
Difference vs. placebo + FBX (95% CI), p-value		0.06 (-0.09, 0.21) p=0.45	0.08 (-0.07, 0.23) p0.12

Abbreviations: FBX, febuxostat; CI, confidence interval; CR, complete resolution; PR, partial resolution

In summary, the efficacy data indicate that lesinurad at the 200 mg dose offers little clinically meaningful benefit and does not represent a major therapeutic breakthrough in the management of hyperuricemia and gout. These limited benefits must be weighed carefully against the risks of the drugs. Approval of the drug could be justified only if the safety data revealed no serious safety signals.

Major Safety Concerns

Safety data from four phase 3 randomized clinical trials submitted in the sponsor's NDA (studies 301, 302, 303, and 304) identified dangerous dose-dependent increases in renal adverse events, major cardiovascular adverse events (MACEs), serious adverse events, and deaths compared with placebo.[9] While these safety signals were most prominent with the 400 mg dose of lesinurad, evidence of unacceptable risks was also apparent at the 200 mg dose.

Renal Toxicity

Preclinical toxicology studies demonstrated that lesinurad is nephrotoxic in rats. FDA reviewers in particular noted:

> Chronic toxicology studies showed evidence of kidney toxicity in rats. … In rats, the dose of 600 mg/kg/day (119 x clinical exposure) was lethal due to kidney toxicity (tubular degeneration and single cell necrosis) and gastrointestinal toxicity. … At the dose of 300 mg/kg/day (36 x clinical exposure), kidney findings were limited to tubular dilatation and changes of clinical chemistry parameters. … [These findings] suggest lesinurad has the potential for kidney and GI tract toxicity. The kidney toxicity observed in the rat would not be likely to be due to uric acid crystalluria or nephrolithiasis, as rats, like most mammals, possess functional uricase, and have low serum uric acid levels (in the range of 1 to 2 mg/dL).[10]

Thus, in rats, lesinurad is a direct nephrotoxin that can damage renal tubular cells. Note that the FDA's expression of the animal dose exposure relative to the proposed human dose appears to lack adjustment for the difference in body surface area, resulting in a misleading inflation of the ratio of the animal dose to the human dose.

The safety data from the phase 3 randomized clinical trials for lesinurad provide overwhelming evidence that the drug causes dangerous acute kidney injury in humans. The mechanisms for this lesinurad-induced renal injury likely include uric-acid-induced nephropathy, as well as direct toxicity to renal tubular cells.

Table 38 from the FDA review for the AAC meeting showed a marked lesinurad dose-related increase in the rate of kidney-related adverse events for the 12-month studies (studies 301, 302, and 304) and the six-month monotherapy study (study 303).[11] A clear dose-response relationship can be seen for the most common renal adverse event in all phase 3 studies, blood creatinine elevation in the pooled safety data for studies 301, 302, and 304. Particularly concerning is the higher incidence of acute renal failure — the most severe form of acute kidney injury — at the 400 mg dose.

[9] *Ibid*. PDF page 12.
[10] *Ibid*. PDF page 6.
[11] *Ibid*. PDF page 117.

Table 38: Renal-Related TEAE in the Controlled Phase 3 Studies

Preferred Term (PT)	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Renal-Related AE	**23 (5%)**	**29 (6%)**	**60 (12%)**	**89 (9%)**	**0**	**19 (18%)**
Blood Creatinine Increased	12 (2%)	22 (4%)	40 (8%)	62 (6%)	0	9 (8%)
Blood Urea Increased	3 (1%)	7 (1%)	7 (1%)	14 (1%)	0	2 (2%)
Renal Failure	6 (1%)	4 (1%)	6 (1%)	10 (1%)	0	3 (3%)
Renal Impairment	0	1 (<1%)	5 (1%)	6 (1%)	0	4 (4%)
Acute Renal Failure	2 (<1%)	0	4 (1%)	4 (<1%)	0	3 (3%)
Chronic Renal Failure	3 (1%)	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (1%)
Urine Output Decreased	0	0	3 (1%)	3 (<1%)	0	0
Acute Prerenal Failure	0	0	2 (<1%)	2 (<1%)	0	0
Creatinine Renal Clearance Decreased	0	0	2 (<1%)	2 (<1%)	0	0

For each PT, subjects are included only once, even if they experienced multiple events with that PT.
Modified Sponsor's Tables 4.17.5.1 and 14.17.5.3; ISS

Table 44 from the FDA review, which summarizes data on the incidence of various degrees of serum creatinine elevation for the phase 3 trials, provides compelling evidence for a dose-response toxicity relationship for lesinurad. Note that under the Kidney Disease: Improving Global Outcomes Clinical Practice guidelines for acute kidney injury, increases in serum creatinine of 1.5 to 1.9 times baseline, 2.0 to 2.9 times baseline, and 3.0 or more times baseline are defined as stage 1, stage 2, and stage 3 acute kidney injury, respectively.[12] An increased incidence of acute kidney injury at all three stages occurred in a dose-dependent manner and was evident even at the 200 mg dose used in studies 301, 302, and 304.[13]

Table 44: SCr by Elevation Category in the Controlled Phase 3 Studies

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr Elevation Category:						
sCr ≥ 1.5 x Baseline	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
sCr ≥ 2.0 x Baseline	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
sCr ≥ 3.0 x Baseline	0	4 (1%)	12 (2%)	16 (2%)	0	4 (4%)

sCr=serum creatinine. Elevation categories are cumulative: subjects can be counted in more than one category, so percentages can sum to >100%. Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication.
Modified Sponsor's Tables 9.1.1.1 and 9.1.1.3; ISS

This same dose-response relationship also was seen when looking at the number of serum creatinine elevations ≥1.5 and ≥2.0 times baseline (see FDA reviewers' Table 45 and 46,

[12] Palevsky PM. Definition of acute kidney injury (acute renal failure). UpToDate. Last updated August 31, 2015. http://www.uptodate.com/contents/definition-of-acute-kidney-injury-acute-renal-failure. Accessed December 3, 2015.
[13] Food and Drug Administration. Briefing document for the October 23, 2015, meeting of the Arthritis Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM467942.pdf. Accessed December 1, 2015. PDF page 130.

respectively).[14] Particularly concerning is the number of serum creatinine elevations that were prolonged or had not resolved by the time of last assessment.

Table 45: SCr Elevation ≥1.5 x Baseline, Number and Reversibility of Changes

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr ↑≥ 1.5 x Baseline						
Number of Pts. With:						
No Elevation	504 (98%)	482 (94%)	437 (86%)	919 (90%)	107(100%)	81 (76%)
At Least 1 Elevation	12 (2%)	29 (6%)	73 (14%)	102 (10%)	0	26 (24%)
1 Elevation	12 (2%)	28 (6%)	52 (10%)	80 (8%)	0	22 (21%)
2 Elevations	0	1 (<1%)	18 (4%)	19 (2%)	0	3 (3%)
>2 Elevations	0	0	3 (1%)	3 (<1%)	0	1 (1%)
Total Number of Elevations	**12**	**30**	**97**	**127**	**0**	**31**
Total # of Resolutions	9 (75%)	27 (90%)	80 (83%)	107 (84%)	0	16 (52%)
# Resolut. S/P Interruption of Study Meds	0	7 (23%)	16 (17%)	23 (18%)	0	1 (3%)
# Resolut. W/O Interrupt. of Study Meds	9 (75%)	20 (67%)	64 (66%)	84 (66%)	0	15 (48%)
Time to Resolution:	**(n=12)**	**(n=30)**	**(n=97)**	**(n=127)**	**(n=0)**	**(n=31)**
1-14 days	1 (8%)	9 (30%)	13 (13%)	22 (17%)	0	1 (3%)
>14-28 days	1 (8%)	3 (10%)	21 (22%)	24 (19%)	0	3 (10%)
>28-56 days	3 (25%)	10 (33%)	25 (25%)	35 (28%)	0	6 (19%)
>56-84 days	2 (17%)	2 (7%)	10 (10%)	12 (9%)	0	3 (10%)
>84 days	2 (17%)	3 (10%)	11 (11%)	14 (11%)	0	3 (10%)
Unresolved at Last Assessment	**3 (25%)**	**3 (10%)**	**17 (18%)**	**20 (16%)**	0	**15 (48%)**

sCr=serum creatinine
Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication. A resolution is defined as a sCr value of ≤ 1.2 x baseline following an elevation. A subject remains elevated until a resolution is observed. Denominators are the total number of elevations in each group.
Modified Sponsor's Tables 9.1.5.1.1 and 9.1.5.1.3; ISS

Table 46: SCr Elevation ≥2 x Baseline, Number and Reversibility of Changes

Variable	Pooled 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Tot. LESU + XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
sCr ↑≥ 2.0 x Baseline						
Number of Pts. With:						
No Elevation	516(100%)	502 (98%)	476 (93%)	978 (96%)	107(100%)	98 (92%)
At Least 1 Elevation	0	9 (2%)	34 (7%)	43 (4%)	0	9 (8%)
1 Elevation	0	9 (2%)	28 (6%)	37 94%)	0	7 (7%)
2 Elevations	0	0	6 (1%)	6 (1%)	0	2 (2%)
>2 Elevations	0	0	0	0	0	0
Total Number of Elevations	**0**	**9**	**40**	**49**	**0**	**11**
Total # of Resolutions	0	8 (89%)	32 (80%)	40 (82%)	0	6 (55%)
# Resolut. S/P Interruption of Study Meds	0	2 (22%)	9 (23%)	11 (22%)	0	1 (9%)
# Resolut. W/O Interrupt. of Study Meds	0	6 (67%)	23 (58%)	29 (59%)	0	5 (46%)
Time to Resolution:	**(n=0)**	**(n=9)**	**(n=40)**	**(n=49)**	**(n=0)**	**(n=11)**
1-14 days	0	5 (56%)	7 (18%)	12 (25%)	0	1 (9%)
>14-28 days	0	0	10 (25%)	10 (20%)	0	0
>28-56 days	0	1(11%)	8 (20%)	9 (18%)	0	4 (36%)
>56-84 days	0	0	5 (13%)	5 (10%)	0	1 (9%)
>84 days	0	2 (22%)	2 (5%)	4 (8%)	0	1
Unresolved at Last Assessment	0	**1 (11%)**	**8 (20%)**	**9 (18%)**	0	**5 (46%)**

sCr=serum creatinine
Baseline is defined as the highest sCr value recorded ≤14 days prior to the first dose of randomized study medication. A resolution is defined as a sCr value of ≤ 1.2 x baseline following an elevation. A subject remains elevated until a resolution is observed. Denominators are the total number of elevations in each group.
Modified Sponsor's Tables 9.1.5.1.1 and 9.1.5.1.3; ISS

[14] *Ibid.* PDF pages 131-132.

An FDA analysis also revealed that lesinurad causes a consistent dose-dependent shift to more severe categories of renal impairment with various baseline levels of renal function, as shown in the following table excerpted from the FDA's PowerPoint slides presented at the AAC meeting:[15]

N(%)	Placebo (n=516)	Lesinurad 200mg+XOI (n=511)	Lesinurad 400mg+XOI (n=510)
Normal→ Mild	19 (10.6%)	29 (14.5%)	45 (22.3%)
Mild → Moderate	8 (3.6%)	15 (7.1%)	24 (11.2%)
Moderate→ Severe	1 (1%)	5 (5.0%)	3 (3.3%)
Mild→ Severe	0	0	2 (1%)

Two subjects who had normal baseline renal function and developed acute kidney failure while taking lesinurad underwent kidney biopsies, both of which revealed acute tubular necrosis (ATN).[16] In both cases, lesinurad cannot be ruled out as the cause for the ATN.

The FDA reviewers noted the following regarding the renal safety data:[17]

> The risk for lesinurad-associated renal toxicity is best evidenced by safety data from the monotherapy Study 303. In this study, treatment with the drug is clearly associated with a marked increase in risk for renal adverse events (18%), including reversible and non-reversible creatinine elevations and serious renal-related adverse events (5%) including acute and chronic renal failure as there were no cases of renal adverse events observed in the placebo group.

But similar, substantial evidence of lesinurad-associated toxicity also was seen in studies 301 and 302.

Importantly, after the protocols for the ongoing phase 3 trials (studies 301, 302, and 304) were amended in June 2013, based on emerging renal safety data, to instruct all subjects to drink two liters of fluid per day, no change was seen in exposure-adjusted incidence rates for renal-related adverse events pre- and post-amendment: 8.4 renal-related adverse events/100 patient-years versus

[15] Food and Drug Administration. Slide presentations for the October 23, 2015, meeting of the Arthritis Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM470236.pdf. Accessed December 1, 2015. PDF page 35.
[16] Food and Drug Administration. Briefing document for the October 23, 2015, meeting of the Arthritis Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM467942.pdf. Accessed December 1, 2015. PDF pages 128-129.
[17] *Ibid*. PDF page 87.

9.5 renal-related adverse events/100 patient-years, respectively, for the 200 mg lesinurad groups; and 17.0 renal-related adverse events/100 patient-years versus 15.5 renal-related adverse events/100 patient-years, respectively, for the 400 mg lesinurad groups.

In addition, real-world use of lesinurad — outside the context of a carefully monitored clinical trial and inevitably for off-label uses — undoubtedly will lead to rates of renal adverse events that exceed those seen in the phase 3 clinical trials. It is thus likely that, if approved, lesinurad will trigger an epidemic of drug-induced acute kidney injury.

On the basis of the preclinical and clinical renal safety data alone, the FDA should not approve the NDA for lesinurad. But the serious safety concerns about lesinurad are not limited to its renal toxicity.

Serious Cardiovascular Safety Concerns

As shown in Table 32 from the FDA review, there was a troubling increase in the number of serious cardiac adverse events between the placebo- and lesinurad-treated subjects in the pooled data for studies 301, 302, and 304, with these adverse events increasing in frequency as the dose of lesinurad increased.[18]

Table 32: SAEs in the Controlled Phase 3 Studies (continued)

System Organ Class/ Preferred Term	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 +XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Cardiac Disorders	**2 (1%)**	**10 (2%)**	**14 (3%)**	**24 (2%)**	**2 (2%)**	**0**
Acute Myocardial Infarction	0	1 (<1%)	4 (1%)	5 (1%)	0	0
Coronary Artery Disease	0	3 (1%)	2 (<1%)	5 (1%)	1 (1%)	0
Cardiac Failure Congestive	0	1 (<1%)	3 (1%)	4 (<1%)	0	0
Myocardial Infarction	1 (<1%)	0	3 (1%)	3 (<1%)	0	0
Angina Pectoris	0	1(<1%)	1 (<1%)	2 (<1%)	0	0
Atrial Fibrillation	0	2 (<1%)	0	2 (<1%)	0	0
Atrial Flutter	0	0	1 (<1%)	1 (<1%)	0	0
Cardiac Arrest	0	1(<1%)	0	1 (<1%)	0	0
Cardiac Failure Acute	0	0	1 (<1%)	1 (<1%)	0	0
Intracardiac Thrombus	0	0	1 (<1%)	1 (<1%)	0	0
Myocardial Ischemia	0	1(<1%)	0	1 (<1%)	0	0
Pericardial Effusion	0	0	0	0	1 (1%)	0
Pulseless Electrical Activity	0	1 (<1%)	0	1 (<1%)	0	0
Arrhythmia	1 (<1%)	0	0	0	0	0

There was also an increase in the number of MACEs between the placebo- and lesinurad-treated subjects for the phase 3 trials, shown in Table 35 of the FDA review (excerpted below):[19]

[18] *Ibid.* PDF page 104.
[19] *Ibid.* PDF page 112.

Table 35: Adjudicated Cardiovascular Treatment-Emergent Adverse Events in the Controlled Phase 3 Studies

	Pooled 12-Month, Studies 301, 302 and 304				6- Month, Monotherapy Study 303	
	PBO + XOI (N=516) n (%) [# Events]	LESU200 + XOI (N=511) n (%) [# Events]	LESU400 + XOI (N=510) n (%) [# Events]	Tot. LESU + XOI (N=1021) n (%) [# Events]	PBO (N=107) n (%) [# Events]	LESU400 mg (N=107) n (%) [# Events]
MACE Events:						
Cardiovascular Death	0	2 (<1%)	2 (<1%)[b]	4 (<1%)[b]	0	1 (1%)
Non-Fatal MI	1 (<1%) [1][a]	2 (<1%) [2]	7 (1%) [7][b]	9 (1%) [9][b]	0	0
Non-Fatal Stroke	3 (1%) [3][a]	0	0	0	0	0
Number of Subjects with MACE Events:	3 (1%) [4]	4 (1%) [4]	8 (2%) [9]	12 (1%) [13]	0	1 (1%) [1]

Pts.= patients; Adjud. = adjudicated; Revascul.= Revascularization; Arrhyth.= Arrhythmia; Periph.= Peripheral
MACE events are defined as CV death, non-fatal MI, and non-fatal stroke
Subjects with multiple CEAC–adjudicated events can be counted in more than one category
[a, b]Two subjects experienced more than 1 MACE event: Subject 301-05345-105 who had a non-fatal MI and a non-fatal stroke in the PBO +XOI group and Subject 302-15003-210 who had a non-fatal MI and subsequent CV death in the LESU400 mg + XOI group.
Adapted Sponsor's Table 4.14.1.1. from ISS and Sponsor's table 16.3.1.3 and 14.3.2.2. from CSR for Study 303

Finally, the point estimates for the exposure-adjusted incidence rate for MACEs (number of subjects with MACEs and number of MACEs) increased with lesinurad exposure, particularly at the 400 mg dose (see Table 36 from the FDA review).[20]

Table 36: Exposure-Adjusted Incidence Rate of MACE in Studies 301, 302, & 304

	PBO + XOI (N=516)[1] (421 PY)[2]	LESU200 + XOI (N=511)[1] (415 PY)[2]	LESU400 + XOI (N=510)[1] (413 PY)[2]	Total LESU + XOI (N=1021)[1] (828 PY)[2]
Number of Subjects with MACE	3	4	8	12
Incidence Rate[3] (95% CI)[4]	0.71 (0.23, 2.21)	0.96 (0.36, 2.57)	1.94 (0.97, 3.87)	1.45 (0.82, 2.56)
Number of MACE	4	4	9	13
Incidence Rate[5] (95% CI)[4]	0.95 (0.36, 2.53)	0.96 (0.36, 2.57)	2.18 (1.13, 4.19)	1.57 (0.91, 2.71)
Number of Subjects with CV Death	0	2	2	4
Incidence Rate (95% CI)		0.48 (0.12, 1.93)	0.48 (0.12,1.94)	0.48 (0.18, 1.29)
Number of Subjects with Non-Fatal MI	1	2	7	9
Incidence Rate (95% CI)	0.24 (0.03, 1.69)	0.48 (0.12, 1.93)	1.70 (0.81, 3.56)	1.09 (0.57, 2.09)
Number of Subjects with Non-Fatal Stroke	3	0	0	0
Incidence Rate (95% CI)	0.71 (0.23, 2.21)			

PY= Patient years; CI = Confidence interval
Treatment-emergent AEs are those that started on or after the first randomized study medication dose date, or those that started prior to the first randomized study medication dose date but worsened during the double-blind treatment period of the study. Subjects with multiple events can be counted in more than one category. MACE events include CV death, non-fatal MI, and non-fatal stroke.
[1]Unique number of subjects in safety population
[2]Person-year = (date of completion/discontinuation - date of first dose of study drug +1)/365.25.
[3]Incidence rate= number of subjects with MACE events per 100 person-years.
[4]The 95% confidence intervals are based on Poisson regression.
[5]Incidence rate = number of MACE events per 100 person-year.
Adapted Sponsor's Table 16.2.1 Ad Hoc IAS

Although the number of MACEs was small, the FDA should assume that the cardiovascular safety signal is real until proven otherwise, particularly for a drug that offers meager benefits and is not a breakthrough treatment for a life-threatening disease.

[20] *Ibid.* PDF page 114.

Other Notable Safety Data

Table 29 from the FDA review reveals that any treatment emergent adverse event (TEAE), any severe TEAE, any serious TEAE, any TEAE leading to study drug discontinuation, and death occurred with higher frequency in the lesinurad-treated subjects, particularly at the 400 mg dose.[21]

Table 29: Safety Overview: Phase 3 Studies

	Combined 12-M, Studies 301, 302 and 304				6-M, Monotherapy Study 303	
	PBO + XOI (N=516)	LESU200 + XOI (N=511)	LESU400 + XOI (N=510)	Total LESU +XOI (N=1021)	PBO (N=107)	LESU400 (N=107)
Any Treatment Emergent Adverse Event (TEAE)	363 (70%)	386 (76%)	407 (80%)	793 (78%)	70 (65%)	83 (78%)
Any Severe TEAE	41 (8%)	47 (9%)	59 (12%)	106 (10%)	4 (4%)	16 (15%)
Any Serious TEAE	29 (6%)	24 (5%)	44 (9%)	68 (7%)	4 (4%)	9 (8%)
Any Serious Renal TEAE	4 (1%)	0	8 (2%)	8 (1%)	0	6 (15%)
Any TEAE Leading to Study Medication Discontinuation	28 (5%)	32 (6%)	48 (9%)	80 (8%)	6 (6%)	20 (19%)
Deaths	0	2 (<1%)	3 (1%)	5 (<1%)	0	1 (1%)

Modified Sponsor's Tables 4.1.1.1, 4.8.1.1, 4.9.1.1 and 4.4.1.1 from the Integrated Safety Summary (ISS); Tables 14.3.1.1.a and 14.3.1.5a from Study 303 CSR

Taken together, the safety data from the pivotal phase 3 clinical trials show that lesinurad is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Therefore, there is sufficient basis for the FDA to refuse approval of the NDA for lesinurad under FDA regulations at 21 C.F.R. § 315.125.

Key Observations From the AAC Meeting

Several aspects of the October 23 AAC meeting were particularly notable. First, none of the members who participated in the meeting were nephrologists or cardiologists.[22] The absence of such experts undermined the credibility of the AAC's review, given that the central safety concerns raised in the FDA's review of the NDA submission for lesinurad involved obvious significant renal toxicity and the troubling cardiovascular safety signal. The deliberations during the AAC meeting appeared to reflect a lack of appreciation by some members of the significance of the renal and cardiovascular safety signals.

Second, despite this lack of expertise in nephrology or cardiology among the AAC members, almost half of the voting members of the AAC — six of 14 members, with one abstaining — concluded that the safety profile of lesinurad 200 mg once daily was *not* adequate to support approval of the drug for treatment of hyperuricemia associated with gout in combination with a

[21] *Ibid.* PDF page 94.
[22] Food and Drug Administration. Meeting roster for the October 23, 2015, meeting of the Arthritis Advisory Committee. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM470234.pdf. Accessed December 2, 2015.

xanthine oxidase inhibitor.[23] The one AAC member, Dr. Eric J. Tchetgen (Associate Professor of Biostatistics and Epidemiologic Methods, Harvard School of Public Health), who had abstained from voting on the earlier question regarding lesinurad's safety, subsequently voted against approval, explaining that he had "discomfort with the safety data or rather the uncertainty around safety."[24]

Pertinent comments made by AAC members who concluded that lesinurad's safety profile was inadequate included the following:

- Peter J. Kaboli, M.D. (Vice Chair, Department of Internal Medicine, University of Iowa Carver College of Medicine; and Chief of Medicine, Iowa City Veterans Affairs Healthcare System): "My main concern with this question is … the narrow therapeutic index: that the minimum effective dose is essentially the same as the maximum safe dose. … That's pretty narrow when you talk about therapeutic indices."[25]

  "I voted no, and mainly because … the narrow therapeutic index of this drug really does concern me that if we have it out in general use we're either going to learn that it's safe or we're going to learn that it's not safe and then we'll take it off the market later. So I really felt conflicted that are we going to have something out there that could benefit some people but puts other people at harm."[26]

- Mara L. Becker, M.D. (Associate Professor of Pediatrics, University of Missouri-Kansas City; and Director, Division of Pediatric Rheumatology, Children's Mercy Kansas City): "I think what I was most interested in was in the plots [in the FDA's slides showing the shift in renal impairment category and the adverse events of special interest in patients with various baseline renal function] to thinking about what baseline renal impairment and the risk of shifting from one to the next through the course of the study[, which] I thought was really intriguing and maybe a little nerve-racking, as we're trying to decide what kind of baseline creatinine clearance is meaningful as far as safety. And I have to say, I kind of agree that a [creatinine clearance] of 45 is not rigorous enough and that actually you see some of those patients with mild-to-moderate renal abnormalities initially being at quite significant risk, and even patients who start normal or mild [renal impairment] do tend to progress to more severe renal impairment over the course of the study."[27]

- Cynthia Chauhan, M.S.W. (Patient Representative): "I don't think the safety profile is adequate, and I think more work needs to be done."[28]

[23] Food and Drug Administration. Webcast recording of the October 23, 2015, meeting of the Arthritis Advisory Committee: Afternoon break to end of meeting. https://collaboration.fda.gov/p70qnrrw5vk/. Accessed December 2, 2015. Starting at 1:58:04.
[24] *Ibid*. Starting at 2:14:37.
[25] *Ibid*. Starting at 1:02:29.
[26] *Ibid*. Starting at 2:04:50.
[27] *Ibid*. Starting at 1:23:20.
[28] *Ibid*. Starting at 2:00:00.

- Beth L. Jonas, M.D. (Director, Rheumatology Fellowship Training Program, University of North Carolina School of Medicine): "My primary concern is that we don't have longer-term studies and that also there is some concern primarily about patients with renal insufficiency, and that gave me cause to worry about safety in that population."[29]

- Robert G. Smith, D.P.M., M.Sc., R.Ph. (Pharmacist, Comprehensive Health Services, Cape Canaveral, Florida): "I voted no primarily because of the renal data, and the patients I deal with are mostly diabetic and they have comorbidities, and it just gives me cause for pause."[30]

Additionally, some members who concluded that lesinurad's safety profile was adequate nevertheless expressed concerns about the drug's safety and the adequacy of the sponsor's proposed plans for monitoring patients for renal toxicity:

- Seth Mark Berney, M.D. (Professor of Medicine and Chief, Division of Rheumatology, University of Arkansas for Medical Sciences): "I have some concerns about the [sponsor's] seemingly arbitrary decision that the creatinine has to double before we worry about stopping the drug. I also have significant reservations about not making specific recommendations [in the drug labeling] about how often to check the creatinine. I think that leaving those decisions up to novices in using uricosurics is very troublesome, keeping in mind that … most of the rheumatologists in the world are novices in using uricosurics."[31]

- Liron Caplan, M.D., Ph.D. (Associate Professor of Medicine, University of Colorado): "I voted yes [on the question regarding lesinurad's safety]. But it was a very tough call. And I think my yes … carries with it a few caveats, and that is … the onus is on the sponsor to demonstrate benefit and safety at the lower estimated creatinine clearance. … Our default action should be not to recommend it be used in folks below creatinine clearances of 60."[32]

In the context of the third question posed to the AAC, there was a discussion of dose-dependent toxicity of lesinurad, the overlapping drug exposure of the 200 mg and 400 mg lesinurad doses, and whether a lower dose given more frequently (for example, 100 mg twice daily) would provide similar efficacy with a better safety profile. During this discussion, the FDA's Dr. Yim noted the following:

> "The concern really gets back to what you were describing, which is if we're very close to what we are considering the maximum tolerated dose, we sometimes make the decision to ask for a change in the dosing regimen before we will approve something to improve the distance between the efficacious dose and the maximum tolerated dose so that we're not quite so close to dropping off the safety curve."[33]

[29] *Ibid.* Starting at 2:01:11.
[30] *Ibid.* Starting at 2:05:20.
[31] *Ibid.* Starting at 1:09:11.
[32] *Ibid.* Starting at 2:01:31.
[33] *Ibid.* Starting at 1:42:27.

Risk-Benefit Assessment and Conclusions

Gout is not a life-threatening disease, and, importantly, there are multiple FDA-approved drugs already on the market. Lesinurad does not offer any major unique or breakthrough benefits compared to these approved therapies, and, in fact, the data for studies 301, 302, and 304 show at best meager clinically meaningful benefits.

In contrast to the limited benefits, the clinical trials have documented very serious safety concerns, the most significant being compelling evidence of dangerous nephrotoxicity and a troubling cardiovascular safety signal. The currently available data thus demonstrate that the risks of the drug far exceed its benefits.

There is no evidence that instructing patients to drink at least two liters of fluid per day and always combining lesinurad with a xanthine oxidase inhibitor will prevent the type of renal injury seen during the clinical trials of lesinurad. Indeed, adverse renal events occurred despite such measures during the phase 3 clinical trials. Moreover, such proposed renal risk mitigation steps presume that the renal toxicity seen in the clinical trials is due only or primarily to uric acid nephropathy. However, given the preclinical animal data and clinical trial data, that assumption is likely false.

In addition, as previously stated, real-world use of lesinurad undoubtedly will lead to rates of renal and other adverse events that exceed those seen in the phase 3 clinical trials.

The only reasonable course of action for the FDA, given the available data, is to reject the AAC's recommendation to approve lesinurad and deny approval of the NDA for the drug. FDA approval — with reliance on warnings in the product labeling, a risk evaluation and mitigation strategy, and postmarket safety studies — would be a reckless approach and would not be in the interests of public health.

Thank you for considering our comments in this important matter.

Sincerely,

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