MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2007

TO: The Zimulti Advisory Committee

FROM: FDA

SUBJECT: **Errata to FDA Background document for the Zimulti Advisory Committee on June 13, 2007**

The Division of Metabolism and Endocrinology Products provides these corrections to the original background package submitted for the Zimulti (rimonabant) Advisory Committee meeting scheduled for June 13, 2007.

The following addenda to the Briefing Document are being made:

1. On page 15 of the briefing document.

Please note the corrected table:

Table 4: Subject Disposition – 1-year Pooled RIO Data – Re-adjudicated Data

DISPOSITION OF PATIENTS	PLACEBO N=1602 N (%)	RIMONABANT 5 MG N=2220 N (%)	RIMONABANT 20 MG N=2176 N (%)
Completed study treatment period	787 (49.1)	943 (42.5)	975 (44.8)
Study treatment discontinuation	815 (50.9)	1277 (57.5)	1201 (55.2)
Main reason for treatment discontinuation:			
Disease progression/lack of efficacy	52 (3.2)	77 (3.5)	51 (2.3)
Recovery	0	0	2 (<0.1)
Adverse event	265 (16.5)	475 (21.4)	574 (26.4)
Poor compliance to protocol	57 (3.6)	103 (4.6)	73 (3.4)
Investigator/subject's request	341 (21.3)	508 (22.9)	391 (18.0)
Subject lost to follow-up	78 (4.9)	80 (3.6)	83 (3.8)
Other reason	22 (1.4)	34 (1.5)	27 (1.3)

2. On page 16 of the briefing document.

Please note the corrected table:

Table 1: Change in Body Weight from Baseline to Year 1 – RIO N.A. and Europe

EFFICACY DATA	RIO NORTH AMERICA PLACEBO N=607	RIO NORTH AMERICA 5 MG N=1214	RIO NORTH AMERICA 20 MG N=1219	RIO EUROPE PLACEBO N=305	RIO EUROPE 5 MG N=603	RIO EUROPE 20 MG N=599
Mean Change (kg) Range	-1.6 -38.7 to 14.6	-2.9** -93.1 to 15.0	-6.3** -46.3 to 26.2	-1.8 -39.0 to 17.0	-3.4* -38.7 to 18.3	-6.6** -42.1 to 14.1
Mean % Change Range	-1.6 -27.4 to 10.1	-2.8 -50.3 to 12.1	-6.2 -40.4 to 26.3	-1.8 -31.0 to 16.6	-3.4 -31.2 to 20.5	-6.6 -39.7 to 13.4
5% Responders N (%)	118 (20.0)	311 (26.1)	578 (48.6)	58 (19.2)	198 (33.2)	303 (50.9)
10% Responders N (%)	50 (8.5)	126 (10.6)	300 (25.2)	22 (7.3)	60 (10.1)	163 (27.4)

*p<0.05; **p<0.001 for mean difference to placebo. Conversion equation: kg x 2.2 = pounds

3. On page 16 of the briefing document.

The weight loss effect in all of the RIO studies by BMI category is provided below.

Table 1: Weight change from baseline by screening category of BMI

Study	Dose	BMI ≥40 kg/m^2		BMI <40 kg/m^2		Treatment-by-BMI stratum interaction
		n	LSM (SE)	n	LSM (SE)	
EFC4733	20mg	143	-6.8 (0.58)	450	-6.49 (0.33)	
EFC4733	PLB	65	-2.69 (0.86)	237	-1.59 (0.45)	
LSM difference from Placebo			**-4.11 [-6.15, -2.07]**		**-4.90 [-6.00, -3.80]**	**p=0.50**
EFC4735	20mg	7	-11.14 (2.1)	337	-6.85 (0.3)	
EFC4735	PLB	4	2.4 (2.78)	330	-1.55 (0.31)	
LSM difference from Placebo			**-13.54 [-20.39, -6.70]**		**-5.30 [-6.15, -4.45]**	**p=0.02**
EFC4736	20mg	9	-4.63 (1.49)	327	-5.34 (0.25)	
EFC4736	PLB	7	0.01 (1.69)	338	-1.47 (0.24)	
LSM difference from Placebo			**-4.65 [-9.06, -0.23]**		**--3.87 [-4.79, -3.19]**	**p=0.73**
EFC4743	20mg	371	-7.79 (0.35)	819	-5.58 (0.23)	
EFC4743	PLB	189	-1.49 (0.48)	401	-1.58 (0.33)	
LSM difference from Placebo			**-6.31 [-7.47, -5.14]**		**-4.00 [-4.80, -3.20]**	**p=0.001**

The treatment-by-BMI (< 40 kg/m^2 and ≥ 40 kg/m^2) stratum interaction for percent change from baseline for RIO North America was -5.18% for BMI ≥ 40 kg/m^2 and -4.4% for BMI < 40 kg/m^2, p=0.29.

4. On page 17 of the briefing document.

Please note:

"The weight regain mean difference was -0.7 kg (p=0.12) between the 5 mg/5 mg group and the 5 mg/placebo group and -4.2 kg (p<0.001) between the 20 mg/20 mg group and the 20 mg/placebo group."

5. On page 19 of the briefing document.

Please note:

RIO-DIABETES			
HbA_{1c}			
Mean change	0.1 (1.0)	-0.1 (1.0)	-0.6 (0.8)
Mean difference (SEM)		-0.2 (0.1)	-0.7 (0.1)
p-value		0.034	<0.001

6. On page 32 of the briefing document.

Please note:

Table 2: Neurological Adverse Events - Pooled RIO studies

AEHLGTN PREFERRED TERM	PLACEBO N=1602 (%)	5 MG N=2220 (%)	20 MG N=2176 (%)
Total # of subjects reporting a symptom	**391 (24.4)**	**535 (24.1)**	**596 (27.4)**
Neurological Disorders NEC	**151 (9.4)**	**227 (10.2)**	**311 (14.3)**
Dizziness	89 (5.56)	138 (6.22)	186 (8.55)
Paresthesia	17 (1.06)	23 (1.04)	37 (1.70)
Hypoaesthesia	14 (0.87)	32 (1.44)	31 (1.42)
Headaches	**247 (15.4)**	**287 (12.9)**	**266 (12.2)**
Headache	203 (12.67)	225 (10.14)	220 (10.11)
Migraine	31 (1.94)	43 (1.94)	36 (1.65)
Mental Impairment Disorders	**21 (1.3)**	**26 (1.2)**	**45 (2.1)**
Memory impairment	7 (0.44)	14 (0.63)	16 (0.74)
Disturbance in attention	10 (0.62)	2 (0.09)	15 (0.69)
Amnesia	8 (0.50)	8 (0.36)	14 (0.64)
Spinal Cord and Nerve Root Disorders	**15 (0.94)**	**29 (1.3)**	**31 (1.4)**
Sciatica	10 (0.62)	23 (1.04)	27 (1.24)
Movement Disorders	**1 (0.06)**	**8 (0.36)**	**24 (1.1)**
Tremor	0	6 (0.27)	21 (0.97)
Peripheral Neuropathies	**19 (1.19)**	**29 (1.31)**	**21 (0.97)**

Subjects receiving the same treatment during the whole study

7. On page 34 of the briefing document.

Please note:

"Three cases of confirmed multiple sclerosis and 2 cases of suspicion of demyelinating disease have been reported from rimonabant trials as of 18 December 2006."