F. Appendix VI: Discontinuations Due to Adverse Events by Subgroup

1. Male vs Female

a) Study MA-14

Table 169: MA-14 Discontinuations Due to Adverse Events, Most Common Male vs Female

				Treatment				
			All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Male (M) Patients, n =			M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =			F=79	F=14	F=17	F=16	F=17	F=15
Discontinued for AE*, n (%)		All	28(17)	7(23)	2 (6)	9 (26)	7 (22)	3 (9)
		Male	12 (14)	5 (29)	2 (12)	5 (28)	0	0
		Female	16 (20)	2 (14)	0	4 (25)	7 (41)	3 (20)
Cardiovascular	**Flushing**	Male	3 (4)	2 (12)	0	1 (6)	0	0
		Female	6 (8)	1 (7)	0	3 (19)	2 (12)	0
Skin and Appendages	**Rash**	Male	3 (4)	0	1 (6)	2 (11)	0	0
		Female	4 (5)	1 (7)	0	1 (6)	2 (12)	0
	Pruritis	Male	1 (1)	0	0	1 (6)	0	0
		Female	2 (3)	0	0	0	2 (12)	0
	Urticaria	Male	2 (2)	0	0	2 (11)	0	0
		Female	1 (1)	0	0	1 (6)	0	0
Body as a Whole	**Asthenia**	Male	1 (1)	1 (6)	0	0	0	0
		Female	2 (3)	0	0	0	1 (6)	1 (7)
Digestive	**Nausea**	Male	1 (1)	1 (6)	0	0	0	0
		Female	2 (3)	0	0	0	1 (6)	1 (7)

* Patients may have reported more than one AE term per discontinuation.

b) Study MA-06

Table 170: MA-06 Discontinuations Due to Adverse Events, Most Common Male vs Female

				Treatment			
			All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =			M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =			F = 106	F = 26	F = 25	F = 33	F = 22
Discontinued for AE*, n (%)		All	40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
		Male	15 (12)	6 (19)	5 (16)	2 (7)	2 (5)
		Female	25 (24)	6 (23)	5 (20)	10 (30)	4 (18)
Body System	**COSTART Term**						
Cardiovascular	**Flushing**	Male	8 (6)	3 (10)	4 (13)	0	1 (3)
		Female	8 (8)	3 (12)	2 (8)	3 (9)	0
Musculoskeletal	**Myalgia**	Male	2 (2)	1 (3)	0	1 (4)	0
		Female	6 (6)	1 (4)	0	1 (3)	4 (18)
Skin and Appendages	**Rash**	Male	2 (2)	0	0	1 (4)	1 (3)
		Female	4 (4)	1 (4)	1 (4)	2 (6)	0
	Pruritis	Male	2 (2)	0	1 (3)	0	1 (3)
		Female	4 (4)	1 (4)	1 (4)	2 (6)	0
	Urticaria	Male	2 (2)	0	1 (3)	0	1 (3)
		Female	2 (2)	0	0	2 (6)	0
Body as a Whole	**Headache**	Male	1 (1)	0	1 (3)	0	0
		Female	3 (3)	1 (4)	0	2 (6)	0

*Patients may have reported more than one AE term per discontinuation

2. Geriatric vs Non-Geriatric

a) Study MA-14

Table 171: MA-14 Discontinuations Due to Adverse Events, Most Common Geriatric vs Non-Geriatric

				Treatment				
			All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Geriatric (G) Patients, n =			G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =			NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
Discontinued for AE*, n (%)		All	28(17)	7(23)	2 (6)	9 (26)	7 (22)	3 (9)
		G	14 (22)	2 (25)	1 (7)	7 (47)	2 (15)	2 (15)
		NG	14 (14)	5 (22)	1 (5)	2 (11)	5 (26)	1 (5)
Cardiovascular	**Flushing**	G	3 (5)	0	0	3 (20)	0	0
		NG	6 (6)	3 (13)	0	1 (5)	2 (11)	0
Skin and	**Rash**	G	7 (11)	1 (2)	1 (7)	3 (20)	2 (15)	0
Appendages		NG	0	0	0	0	0	0
	Pruritis	G	1 (2)	0	0	1 (7)	0	0
		NG	2 (2)	0	0	0	2 (11)	0
	Urticaria	G	3 (5)	0	0	3 (20)	0	0
		NG	0	0	0	0	0	0
Body as a Whole	**Asthenia**	G	0	0	0	0	0	0
		NG	3 (3)	1 (4)	0	0	1 (5)	1 (5)
Digestive	**Nausea**	G	1 (2)	1 (13)	0	0	0	0
		NG	2 (2)	0	0	0	1 (5)	1 (5)

* Patients may have reported more than one AE term per discontinuation

b) Study MA-06

Table 172: MA-06 Discontinuations Due to Adverse Events, Most Common Geriatric vs Non-Geriatric

				Treatment			
			All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Geriatric (G) Patients, n =			G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =			NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
Discontinued for AE*, n (%)		**All**	40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
		G	14 (18)	5 (28)	7 (35)	2 (12)	0
		NG	26 (17)	7 (18)	3 (8)	10 (23)	6 (17)
Body System	**COSTART Term**						
Cardiovascular	**Flushing**	G	7 (9)	1 (6)	5 (25)	1 (6)	0
		NG	9 (6)	5 (13)	1 (3)	2 (5)	1 (3)
Musculoskeletal	**Myalgia**	G	1 (1)	1 (6)	0	0	0
		NG	7 (4)	1 (3)	0	2 (5)	4 (11)
Skin and	**Rash**	G	1 (1)	0	1 (5)	0	0
Appendages		NG	5 (3)	1 (3)	0	3 (7)	1 (3)
	Pruritis	G	2 (3)	1 (6)	1 (5)	0	0
		NG	4 (3)	0	1 (3)	2 (5)	1 (3)
	Urticaria	G	2 (3)	0	1 (5)	1 (6)	0
		NG	2 (1)	0	0	1 (2)	1 (3)
Body as a	**Headache**	G	2 (3)	1 (6)	0	1 (6)	0
Whole		NG	2 (1)	0	1 (3)	1 (2)	0

*Patients may have reported more than one AE term per discontinuation

G. Appendix VII Serious Adverse Events

1. Study MA-07

Table 173: MA-07 Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
01-009	M	72	Myocardial infarction (MI)	CV	350	NR	N
01-021	M	37	Arteriosclerotic coronary artery disease	CV	112	NR	Y
01-030	F	57	Coronary occlusion	CV	63	NR	N
02-007	M	64	MI/cardiac arrest/death	CV	Unk	NR	Y (death)
02-032	M	61	Unstable angina, Right bundle branch block	CV	196	NR	N
02-034	M	52	Abdominal aortic aneurysm	CV	224	NR	N
06-008	F	80	MI/cardiac arrest/death	CV	350	NR	N (completed)
06-011	M	70	Death/cardiac Arrest	CV	Unk	NR	Y (death)
09-003	M	74	MI	CV	77	NR	N
11-023	F	69	Bradycardia/syncope/hypotension	CV	154	NR	N
13-001	M	54	MI	CV	287	NR	N
16-026	M	81	Stroke	CV	112	NR	N
17-006	F	76	Atrial fibrillation (A fib)	CV	91	NR	N
18-002	F	82	MI	CV	126	NR	N
18-010	M	62	Coronary occlusion	CV	91	NR	N
19-015	F	81	Stroke	CV	133	NR	Unknown
21-012	M	61	A fib/mitral regurgitation	CV	49	NR	N
28-010	M	38	Coronary occlusion	CV	364	NR	N (Completed)
28-013	M	47	Angina	CV	217	NR	N
31-026	M	70	Hematoma	CV	42	NR	N
34-001	M	71	Claudication/Peripheral vascular disease (PVD)	CV	119	NR	N
34-001	M	71	Ventricular tachycardia (VT)	CV	224	NR	N
34-001	M	71	Coronary occlusion	CV	224	NR	N
34-001	M	71	Left carotid artery stenosis	CV	315	NR	N
34-005	M	70	Thrombosed left femoral-popliteal bypass	CV	77	NR	N
34-008	F	67	Unstable angina	CV	112	NR	Y
36-006	M	62	PVD/bilateral internal iliac artery stenosis	CV	168	NR	N
38-005	M	70	Non-sustained VT	CV	210	NR	N
39-003	M	70	Coronary occlusion/Aortic stenosis	CV	238	NR	N
39-003	M	70	Non-sustained VT	CV	238	NR	N
45-003	M	60	Coronary occlusion	CV	329	NR	N
45-009	M	66	Coronary occlusion	CV	322	NR	N
45-014	F	81	Left Cerebral vascular accident post-op	CV	161	NR	N
01-020	M	61	Diverticular hemorrhage	GI	280	NR	N
01-030	F	57	Biliary dyskinesia	GI	266	NR	N
07-021	F	63	Hematemesis/Mallory Weis tear/hiatal hernia (HH)/reflux esophagitis	GI	77	Possibly	Y
12-016	M	64	Appendicitis	GI	217	NR	N
12-016	M	64	Post-operative (post-op) ileus	GI	217	NR	N
12-018	F	65	Lower Gastrointestinal (GI) bleed/cecal arteriovenous malformation	GI	189	Remote	N
20-002	M	45	Cholecystitis/cholelithiasis	GI	28	NR	N
20-002	M	45	Acute appendicitis	GI	161	NR	N
21-025	M	50	Diverticulitis	GI	42	NR	N
22-015	F	78	Death/perforated duodenal ulcer/stomach ulcer	GI	357	Remotely	Y (death)

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
30-020	F	70	Non-cardiac chest pain/ulcerated antritis/HH/ulcerative esophagitis	GI	175	Definitely	Y
31-006	M	75	Nausea/dizziness	GI/Ner	294	NR	N
38-002	M	63	Ischemic colitis/diverticulitis	GI	259	NR	N
12-017	F	67	Lumbar spondylolithesis/Left hip pain	MS	49	NR	N
31-006	M	75	Lumbar stenosis/claudication	MS	294	NR	N
32-003	F	78	Fractured pelvis	MS	119	NR	N
38-005	M	70	Pelvic fracture	MS	210	NR	N
45-010	M	66	Left shoulder rotator cuff tear	MS	168	NR	N
45-014	F	81	Left groin pain/Degenerative joint disease – hip	MS	161	NR	N
02-038	M	50	Suicidal ideation	Body	350	NR	N
06-023	M	76	Cellulitis	Body	252	NR	N
28-006	M	75	Cellulitis	Body	254	NR	N
40-007	M	64	Gastrointestinal cancer	Body	280	NR	N
40-007	M	64	Wound infection	Body	280	NR	N
01-030	F	57	Pleurisy/pneumonia	Resp	266	NR	N
28-010	M	38	Pneumonia	Resp	364	NR	N (Completed)
31-026	M	70	Pneumonia	Resp	7	NR	N
18-002	F	82	Hyperkalemia	MAN	140	NR	N
18-002	F	82	Acute-on-chronic renal insufficiency	MAN	140	NR	N
34-004	M	58	Diabetes mellitus	MAN	84	Probably	Y
05-004	M	55	Peyronie's plaque	Uro	238	NR	N
23-009	F	58	Uterine fibroids	Uro	175	NR	N
35-007	M	78	Bilateral hydronephrosis/Increased BUN/Cr	Uro	273	NR	Y
01-020	M	61	Anemia requiring transfusion	HAL	280	NR	N
45-014	F	81	Post-op anemia requiring transfusion	HAL	161	NR	N
07-023	M	35	Anxiety/depression	Ner	336	NR	N
30-011	F	56	Labrynthitis	SS	77	NR	N

CV = cardiovascular, GI = gastrointestinal, HAL = hematologic and lymphatic, Resp = respiratory, Body = body as a whole, Uro = urologic, Ner = nervous, MS = musculoskeletal, MAN = metabolic and nutritional, SS = special senses

2. MA-07 Extension Study

Table 174: 48-Week Extension Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
06-007	M	79	MI/heart failure	CV	462	NR	N
07-017	M	54	Mitral regurgitation	CV	266	Remotely	Y
11-023	F	70	Carotid stenosis	CV	574	NR	N
18-002	F	84	Congestive Heart Failure (CHF)	CV	413	NR	N
18-016	F	81	CHF/atrial fibrillation (A fib)	CV	686	NR	N
20-004	M	72	MI	CV	714	NR	Y
22-009	F	75	A fib	CV	399	NR	N
22-009	F	75	Coronary occlusion	CV	399	NR	N
22-009	F	75	CHF	CV	462	MR	N
22-016	F	70	Chest pain/atypical angina	CV	462	NR	N
27-005	F	54	Unstable angina/coronary occlusion	CV	420	NR	N
27-014	M	44	AVM brain/resection	CV	455	NR	Y
34-001	M	72	Near syncope/hypotension	CV	553	NR	N
45-009	M	67	Coronary occlusion	CV	462	NR	N
45-010	M	67	MI	CV	479	NR	N
06-010	M	83	Spinal stenosis	MS	371	NR	N
12-005	F	68	Broken ankle	MS	567	NR	N
22-006	F	74	DJD left knee	MS	476	NR	N
24-007	M	51	Pseudogout right knee	MS	469	NR	N
30-005	M	73	Herniated disc	MS	448	NR	N
38-006	M	68	Degenerative arthritis right knee	MS	574	NR	N
09-003	M	75	Cholelithiasis/biliary colic	Dig	476	NR	N
18-010	M	62	Cholelithiasis/cholecystitis	Dig	644	Possibly	N
07-017	M	54	Chronic Anemia requiring transfusion (bleeding hemorrhoids)	HAL	266	Remotely	Y
22-009	F	75	Anemia requiring transfusion	HAL	462	NR	N
12-012	F	72	Cataracts	SS	399	Remotely	N
26-007	F	77	Cataract	SS	560	NR	N
06-020	M	75	Ventral hernia	Body	511	NR	N
10-023	M	68	Left femoral-popliteal aneurysm secondary to trauma (MVA)	Neuro	427	NR	N
20-004	M	72	COPD	Resp	714	NR	Y

H. Appendix VIII: Treatment Emergent Laboratory Abnormalities by Subgroup

1. ALT

a) Study MA-14

Table 175: MA-14 ALT Elevations from Baseline, Male vs Female

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
ALT >normal, n (%)	M	19 (22)	4 (24)	0	6 (33)	6 (40)	3 (17)
ALT >normal, n (%)	F	15 (19)	2 (14)	5 (29)	7 (44)	1 (6)	0
ALT >2 X ULN, n (%)	M	1 (1)	0	0	0	1 (7)	0
ALT >2 X ULN, n (%)	F	3 (4)	1 (7)	1 (6)	1 (6)	0	0
ALT >3 X ULN, n (%)	M	1 (1)	0	0	1 (6)	0	0
ALT >3 X ULN, n (%)	F	1 (1)	0	0	1 (6)	0	0

Table 176: MA-14 ALT Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Geriatric (G) Patients, n =		G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =		NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
ALT >normal, n (%)	G	9 (14)	1 (13)	1 (7)	3 (20)	3 (23)	1 (8)
ALT >normal, n (%)	NG	25 (25)	5 (22)	4 (20)	10 (53)	4 (21)	2 (10)
ALT >2 X ULN, n (%)	G	2 (3)	0	0	1 (7)	1 (8)	0
ALT >2 X ULN, n (%)	NG	4 (4)	1 (4)	1 (5)	2 (11)	0	0
ALT >3 X ULN, n (%)	G	0	0	0	0	0	0
ALT >3 X ULN, n (%)	NG	2 (2)	0	0	2 (11)	0	0

b) Study MA-06

Table 177: MA-06 ALT Elevations from Baseline, Male vs Female

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =		M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =		F = 106	F = 26	F = 25	F = 33	F = 22
ALT >normal, n (%)	M	15 (12)	2 (6)	6 (19)	4 (14)	3 (8)
ALT >normal, n (%)	F	13 (12)	1 (4)	3 (12)	5 (15)	4 (18)
ALT >2 X ULN, n (%)	M	2 (2)	0	1 (3)	1 (4)	0
ALT >2 X ULN, n (%)	F	2 (2)	0	0	0	2 (9)
ALT > 3 X ULN, n (%)	M	0	0	0	0	0
ALT >3 X ULN, n (%)	F	1 (1)	0	0	0	1 (5)

Table 178: MA-06 ALT Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Geriatric (G) Patients, n =		G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =		NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
ALT >normal	G	10 (13)	3 (17)	3 (15)	4 (24)	0
ALT >normal	NG	18 (12)	0	6 (16)	5 (11)	7 (19)
ALT >2 X ULN	G	0	0	0	0	0
ALT >2 X ULN	NG	4 (5)	0	1 (3)	1 (2)	2 (6)
ALT >3 X ULN	G	0	0	0	0	0
ALT >3 X ULN	NG	1 (1)	0	0	0	1 (3)

2. AST

a) Study MA-14

Table 179: MA-14 AST Elevations from Baseline, Male vs Female

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
AST >normal, n (%)	M	44 (52)	9 (53)	3 (18)	11 (61)	14 (93)	7 (39)
AST >normal, n (%)	F	34 (43)	8 (57)	6 (35)	12 (75)	7 (41)	1 (7)
AST >2 X ULN, n (%)	M	5 (6)	0	0	3 (17)	2 (13)	0
AST >2 X ULN, n (%)	F	6 (8)	2 (14)	1 (6)	2 (13)	1 (6)	0
AST >3 X ULN, n (%)	M	2 (2)	0	0	1 (6)	1 (7)	0
AST >3 X ULN, n (%)	F	2 (3)	0	0	2 (13)	0	0

Table 180: MA-14 AST Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Geriatric (G) Patients, n =		G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =		NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
AST >normal, n (%)	G	27 (43)	3 (38)	3 (21)	9 (60)	9 (69)	4 (31)
AST >normal, n (%)	NG	51 (50)	14 (61)	6 (30)	14 (74)	12 (63)	4 (20)
AST >2 X ULN, n (%)	G	4 (6)	1 (13)	0	1 (7)	2 (15)	0
AST >2 X ULN, n (%)	NG	7 (7)	1 (4)	1 (5)	4 (21)	1 (5)	0
AST >3 X ULN, n (%)	G	2 (3)	0	0	1 (7)	1 (8)	0
AST >3 X ULN, n (%)	NG	2 (2)	0	0	2 (11)	0	0

b) Study MA-06

Table 181: MA-06 AST Elevations from Baseline, Male vs Female

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =		M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =		F = 106	F = 26	F = 25	F = 33	F = 22
AST >normal	M	43 (33)	6 (19)	12 (38)	9 (32)	16 (41)
AST >normal	F	22 (21)	5 (19)	7 (28)	5 (15)	5 (23)
AST >2 X ULN	M	2 (2)	0	1 (3)	1 (4)	0
AST >2 X ULN	F	4 (4)	0	1 (<1)	1 (3)	2 (9)
AST >3 X ULN	M	0	0	0	0	0
AST >3 X ULN	F	2 (2)	0	1 (<1)	0	1 (5)

Table 182: MA-06 AST Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Geriatric (G) Patients, n =		G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =		NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
AST >normal	G	21 (26)	3 (17)	5 (25)	6 (35)	7 (28)
AST >normal	NG	44 (28)	8 (21)	14 (38)	8 (18)	14 (39)
AST >2 X ULN	G	1 (1)	0	1 (5)	0	0
AST >2 X ULN	NG	5 (3)	0	1 (3)	2 (5)	2 (6)
AST >3 X ULN	G	1 (1)	0	1 (3)	0	0
AST >3 X ULN	NG	1 (1)	0	0	0	1 (3)

3. FBS

a) Study MA-14

Table 183: MA-14 FBS Elevations from Baseline, Male vs Female

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
FBS >normal	M	45 (53)	8 (47)	7 (41)	13 (72)	10 (67)	7 (39)
FBS >normal	F	41 (52)	10 (71)	14 (82)	9 (56)	7 (41)	1 (7)
FBS >1.3 X ULN	M	8 (9)	1 (6)	0	3 (17)	2 (13)	2 (11)
FBS >1.3 X ULN	F	7 (9)	1 (7)	2 (12)	1 (6)	3 (18)	0
FBS >2 X ULN	M	1 (1)	0	0	1 (6)	0	0
FBS >2 X ULN	F	0	0	0	0	0	0

Table 184: MA-14 FBS Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment				
		All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Geriatric (G) Patients, n =		G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =		NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
FBS >normal	G	36 (57)	6 (75)	9 (64)	9 (60)	7 (54)	5 (38)
FBS >normal	NG	50 (50)	12 (52)	12 (60)	13 (68)	10 (53)	3 (15)
FBS >1.3 X ULN	G	8 (13)	2 (25)	1 (7)	1 (7)	2 (15)	2 (15)
FBS >1.3 X ULN	NG	7 (7)	0	1 (5)	3 (16)	3 (16)	0
FBS >2 X ULN	G	0	0	0	0	0	0
FBS >2 X ULN	NG	1 (1)	0	0	1 (5)	0	0

b) Study MA-06

Table 185: MA-06 FBS Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment			
		All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT Geriatric (G) Patients, n =		G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =		NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
FBS >normal	G	49 (61)	11 (61)	8 (40)	14 (82)	16 (64)
FBS >normal	NG	65 (42)	26 (67)	18 (49)	12 (27)	9 (25)
FBS >1.3 X ULN	G	13 (16)	2 (11)	2 (10)	3 (18)	6 (24)
FBS >1.3 X ULN	NG	21 (13)	10 (26)	6 (16)	3 (7)	2 (6)
FBS >2 X ULN	G	2 (3)	0	1 (5)	0	1 (4)
FBS >2 X ULN	NG	2 (1)	1 (3)	1 (3)	0	0

4. Phosphorous

a) Study MA-14

Table 186: MA-14 Phosphorous Elevations from Baseline, Male vs Female

			Treatment				
		All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
Phosphorous <normal, n (%)	M	52 (61)	13 (76)	16 (94)	13 (72)	9 (60)	1 (6)
Phosphorous <normal, n (%)	F	18 (23)	4 (29)	8 (47)	5 (31)	1 (6)	0
Phosphorous <2 X LLN, n (%)	M	12 (14)	4 (24)	4 (24)	2 (11)	2 (13)	0
Phosphorous <2 X LLN, n (%)	F	2 (3)	0	1 (6)	1 (6)	0	0

Table 187: MA-14 Phosphorous Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Geriatric (G) Patients, n =		G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =		NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
Phosphorous <normal, n (%)	G	21 (33)	2 (25)	9 (64)	7 (47)	3 (23)	0
Phosphorous <normal, n (%)	NG	49 (49)	15 (65)	15 (75)	11 (58)	7 (37)	1 (5)
Phosphorous <2 X LLN, n (%)	G	3 (5)	0	2 (10)	1 (7)	0	0
Phosphorous <2 X LLN, n (%)	NG	11 (11)	4 (17)	3 (15)	2 (11)	2 (11)	0

b) Study MA-06

Table 188: MA-06 Phosphorous Decreases from Baseline, Male vs Female

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =		M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =		F = 106	F = 26	F = 25	F = 33	F = 22
Phosphorous <normal	M	34 (26)	11 (35)	11 (34)	7 (25)	5 (13)
Phosphorous <normal	F	14 (13)	4 (15)	3 (12)	6 (18)	1 (5)
Phosphorous <2 X LLN	M	4 (3)	2 (6)	1 (3)	1 (4)	0
Phosphorous <2 X LLN	F	1 (1)	1 (4)	0	0	0

Table 189: MA-06 Phos Decreases from Baseline, Geriatric vs Non-Geriatric

			Treatment			
		All	Advi/20	Advi/40	Niaspan	Lovastatin
ITT Geriatric (G) Patients, n =		G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =		NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
Phosphorous <normal	G	13 (16)	5 (28)	4 (2)	2 (12)	2 (8)
Phosphorous <normal	NG	35 (22)	10 (26)	10 (27)	11 (25)	4 (11)
Phosphorous <2 X LLN	G	1 (1)	1 (6)	0	0	0
Phosphorous <2 X LLN	NG	4 (3)	2 (5)	1 (3)	1 (2)	0

5. CPK

a) Study MA-14

Table 190: MA-14 CPK Elevations from Baseline, Male vs Female

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
CPK >normal	Male	40 (47)	7 (41)	9 (53)	9 (50)	5 (33)	10 (56)
CPK >normal	Female	25 (32)	3 (21)	6 (35)	5 (31)	8 (47)	3 (20)
CPK >5 X ULN	Male	2 (2)	1 (6)	0	1 (6)	0	0
CPK >5 X ULN	Female	1 (1)	1 (7)	0	0	0	0

Table 191: MA-14 CPK Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment				
Randomized Geriatric (G) Patients, n =		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Non-Geriatric (NG) Patients, n =		G = 63 NG = 101	G=8 NG=23	G=14 NG=20	G=15 NG=19	G=13 NG=19	G=13 NG=20
CPK >normal	G	21 (33)	1 (13)	4 (29)	7 (47)	4 (31)	5 (38)
CPK >normal	NG	44 (44)	9 (39)	11 (55)	7 (37)	9 (47)	8 (40)
CPK >5 X ULN	G	2 (3)	1 (13)	0	1 (7)	0	0
CPK >5 X ULN	NG	1 (1)	1 (4)	0	0	0	0

b) Study MA-06

Table 192: MA-06 CPK Elevations from Baseline, Geriatric vs Non-Geriatric

			Treatment			
ITT Geriatric (G) Patients, n =		All	Advi/20	Advi/40	Niaspan	Lovastatin
ITT Non-Geriatric (NG) Patients, n =		G = 80 NG = 156	G = 18 NG = 39	G = 20 NG = 37	G = 17 NG = 44	G = 25 NG = 36
CPK >normal	G	24 (30)	3 (17)	8 (40)	4 (24)	9 (36)
CPK >normal	NG	51 (33)	15 (38)	14 (38)	9 (20)	13 (36)
CPK >5 X ULN	G	0	0	0	0	0
CPK >5 X ULN	NG	1 (1)	0	0	1 (2)	0

APPEARS THIS WAY
ON ORIGINAL

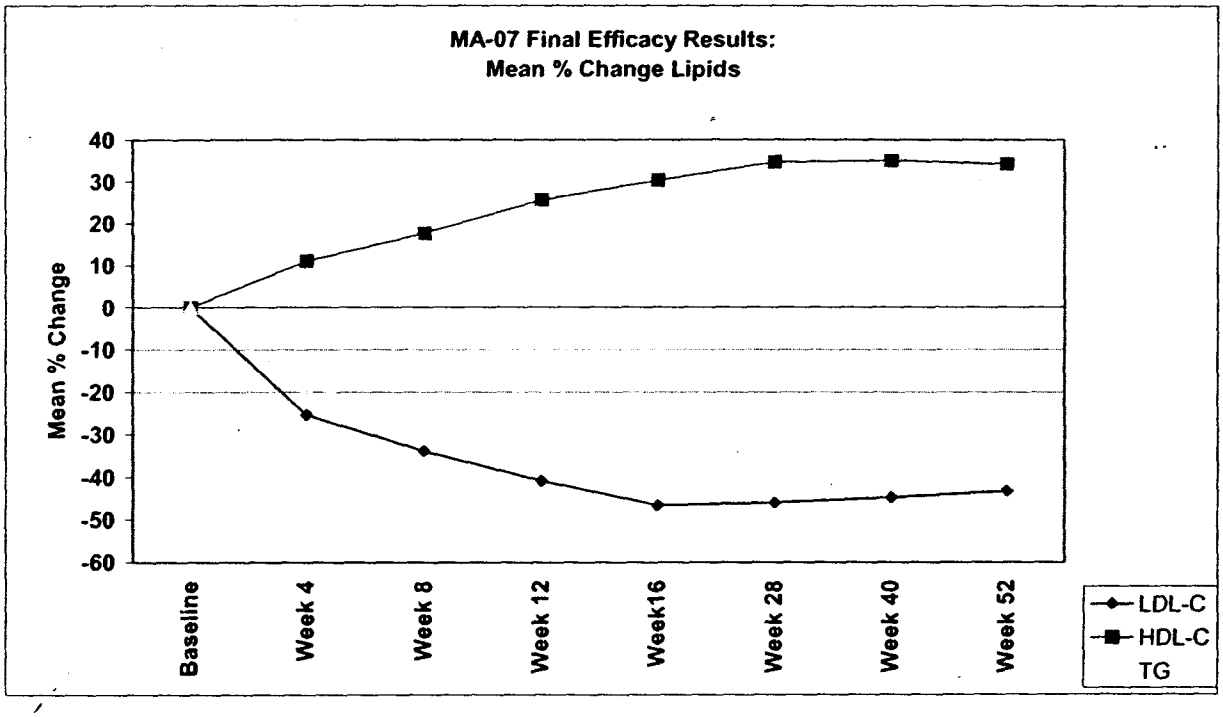
I. Appendix IX: Final Efficacy Results for MA-07

The mean percent change from baseline in LDL-C, HDL-C, and TG for observed-cases until study completion (Week 52) are as follows:

Table 193: MA-07 Final Results Mean % Change from Baseline in Lipid Parameters, Overall

			Week						
		Baseline	4	8	12	16	28	40	52
Advicor dose (mg/mg)			500/10	1000/20	1500/30	2000/40	2000/40	2000/40	2000/40
LDL-C	n	814	753	705	676	655	604	568	550
	Mean	195.3	-25.3	-33.8	-40.8	-46.6	-45.9	-44.7	-43.2
	SE	1.38	0.45	0.54	0.61	0.62	0.70	0.69	0.69
HDL-C	n	814	753	705	676	655	604	570	550
	Mean	47.6	+11.1	+17.7	+25.6	+30.3	+34.7	+35.0	+34.2
	SE	0.4	0.52	0.67	0.79	0.82	0.86	0.96	1.05
TG	n	814	753	706	676	655	604	570	550
	Mean	199.4	-15.6	-26.0	-34.4	-41.2	-39.5	-37.1	-39.5
	SE	3.26	1.01	1.01	0.91	0.97	1.00	1.47	1.16

Figure 15: MA-07 Final Mean % Change Lipids



IX. References

[1] Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256 (20):2823-2828.
[2] Castelli WP, Anderson K, Wilson PWF, Levy D. Lipids and risk of coronary heart disease. The Framingham study. Ann Epidemiol 1992; 2:23-28.
[3] Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251 (3):351-364.
[4] Frick MH, Elo O, Haapa K, Heinonen O, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa J, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila E. Helsinki heart study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-1245.
[5] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-1307.
[6] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 1998;279 (20):1615-1622.
[7] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389.
[8] The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-1357.
[9] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun CC, Davis BR, Braunwald E for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-1009.
[10] Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. JAMA 1986;256 (20):2835- 2838.
[11] Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999;341:410-418.
[12] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education

Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285 (19):2486-2497.
[13] Pasternak RC, Brown LE, Stone PH, Silverman DI, Gibson CM, Sacks FM, for the Harvard Atherosclerosis Reversibility Project (HARP) Study Group. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. Ann Intern Med. 1996; 125:529-540.
[14] Brown BG, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990; 323:1289-1298.
[15] Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987; 257(23):3233-3240.
[16] Brown BG, Brockenbrough A, Zhao XQ, Dowdy AA, Monick EA, Frechette EEH, Poulin DC, Rocha AL. Very intensive lipid therapy with lovastatin, niacin, and colestipol for prevention of death and myocardial infarction: A 10-year Familial Atherosclerosis Treatment Study (FATS) follow-up. Circulation 1998; 98:I-635.
[17] Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990;264 (1):71-75.
[18] Medical Economics Company Inc. Mevacor Tablets (Merck) [2001]. In Physicians' Desk Reference PDR Electronic Library. [Online]. 2001 Physicians' Desk Reference. <http://www.pdrel.com/> ["Mevacor"] [2001, Feb. 08].
[19] Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, Langendorfer A, Nast DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results. Arch Intern Med 1991;151:43-49).
[20] Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, Higgins J, Langendorfer A, Nash DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results: Two-year efficacy and safety follow-up. Am J Cardiol 1994;74:667-673.
[21] Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, Lesperance J, the CCAIT Study Group. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 1994;89:959-968.
[22] Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, DeBoer LWV, Mahrer PR, Masteller MJ, Vailas LI, Alaupovic P, Hirsch LJ, and the MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med 1993;119:969-976.
[23] Furberg CD, Adams HP, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA, Young B for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation 1994;90:1679-1687.

[24] American Society of Health-System Pharmacists, Inc. Niacin. (2001). In Stat!Ref Medical Reference Winter 2001. [Online]. AHFS Drug Information 2000. <http://www.weblern.cder.fda.gov> ["niacin'] [2001, Feb. 12].
[25] Medical Economics Company Inc. Niaspan Extended-Release Tablets (Kos) [2001]. In Physicians' Desk Reference PDR Electronic Library. [Online]. 2001 Physicians' Desk Reference. <http://www.pdrel.com> ["Niaspan"] [2001, Feb. 08].
[26] The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975; 231 (4):360-381.
[27] Canner PL, Berge KTG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986; 8 (6):1245-1255.
[28] Cashin-Hemphill L, Mack WJ, Pogoda J, Sanmarco ME, Azen SP, Blankenhorn DH. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. JAMA 1990; 264 (23):3013-3017.
[29] The Lovastatin Pravastatin Study Group. A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. Am J Cardiol 1993;71:810-815.
[30] Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: the Framingham Offspring Study. Ann Intern Med. 1998;128:524-533.
[31] Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. Lancet 1980;1:1373-1376.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anne Pariser
7/11/01 12:05:33 PM
MEDICAL OFFICER

Mary Parks
7/11/01 01:08:04 PM
MEDICAL OFFICER

David Orloff
7/12/01 06:26:55 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

12-Month Safety Update to NDA 21-249

Sponsor:	**Kos Pharmaceuticals, Inc.**
Drug:	**Advicor (niacin extended-release/lovastatin immediate-release) tablets**
Submission Date:	**27-Sept-2001**
Completion Date:	**18-Oct-2001**
Author:	**Anne Pariser, M.D.** **Medical Officer, DMEDP, HFD-510**

I. NDA 21-249 12-Month Safety Update

A 12-month safety update to NDA 21-249 was submitted on 27-Sept-2001, which provides additional safety information on patients completing the MA-07 long-term safety study 48-week extension, and on patients completing the MA-09 open-label extension study. Also included are 2 Serious Adverse Event reports from the ongoing [redacted] study comparing [redacted] conducted under IND [redacted]

A. Protocol MA-98-010407

1. Study Design for MA-07 Extension Study

a) Study Design

Protocol MA-98-010407 (MA-07) "A Long-term, open-label, multi-center trial of the safety and efficacy of Advicor in patients with dyslipidemia" was a 52-week, open-label, uncontrolled study of Advicor (a combination tablet of niacin extended-release/lovastatin immediate-release) conducted at 41 sites nationally. The study evaluated the safety and efficacy of Advicor in 814 patients with Type IIa and IIb hyperlipidemia and LDL-C levels warranting treatment per NCEP II guidelines. Patients completing the 52-week MA-07 study were offered enrollment in the 48-week extension of MA-07. As the extension study was a continuation of MA-07, the study design was the same as for the initial 52 weeks of the study. 454 patients continued in the 48-extension study.

b) Study Objectives

The purpose of the study was to determine the long-term safety and efficacy of Advicor. The primary efficacy endpoint was mean percent change from baseline in LDL-C. Secondary endpoints were mean percent changes from baseline in TC, HDL-C, TG, TC/HDL-C ratio, LDL-C/HDL-C ratio, Lp(a), and the number of risk factors pre- and post-treatment. Safety endpoints included changes from baseline in chemistry, hematology, and urinalysis tests, and adverse events.

c) Study Medication

All patients received Advicor once daily at bedtime. Patients were continued on the same dose of Advicor as they were receiving in the 52-week study. In most cases, this was Advicor 2000/40; however, the dose could be adjusted down by the Investigator for safety and tolerability. There was no comparator arm.

2. Results

Four hundred fifty-four (454) patients from the original 52-week MA-07 study were rolled over (enrolled) into the extension study between 17-Sept-1998 and 28-Apr-2001 (date of entry into original MA-07 52-week study).

a) Baseline Demographics

An update to the demographic data for patients completing the extension study was not provided.

b) Patient Disposition

The mean duration of study drug exposure for all 814 patients participating in MA-07 was 66.2 weeks. Three hundred ninety-seven (397) of the 454 patients (87%) completed the study. Fifty-seven (57) of the 454 patients (13%) withdrew from the study prior to completion, and 32 of the 57 dropouts were due to AEs. The reasons for patient discontinuations are summarized in the following table (patients discontinued from the original 52-week study are presented for comparison purposes)

Table 1: 48-Week Extension Study Patients Discontinued

	52-Week	48-Week Extension
Patients, n =	814	454
Number of Withdrawals, n (%)	264 (32)	57 (13)
Reason for Dropout		
Adverse Event	188 (23)	32 (7)
Withdrew Consent	23 (3)	9 (2)
Lost to Follow Up	19 (2)	6 (1)
Other	34 (4)	10 (2)

Fewer patients discontinued from the 48-week extension study vs the original 52-week study overall and for AEs. This is not unexpected as patients continuing in the extension study had demonstrated compliance and tolerance of study medication.

3. Efficacy Results

No efficacy information was included in this update.

4. Safety Results

This safety update includes the final safety information on the 454 patients who completed the 48-week extension study.

a) Adverse Events

There were 371 different Adverse Events (AE) terms reported by 789 of the 814 patients (97%) at any time during the study. Adverse Events reported during the extension phase were similar to those reported during the initial 52-week study and the Mar-2001 safety update (previously reported in the NDA review dated 22-Jul-2001). Flushing continued to be the most commonly reported AE, reported by 65% of patients at any time during the study. Other frequently reported AEs were infection (28%), pain (21%), pruritus (19%), rash (13%), headache (13%), nausea (12%), and diarrhea (12%). There did not appear to be a substantial change in the types or frequencies of AEs reported during the extension study. The most commonly reported AEs (≥5%) are listed in the following table [A list of common (≥2%) AEs is in the Appendix]

Table 2: MA-07 Incidence of Most Common (≥5%) Adverse Events at Jan-2001, Mar-2001 and Sep-2001 Updates

Patients, n =		Jan-2001 814	Mar-2001 814	Sep-2001 814
Body System	**COSTART Term**			
Body as a Whole	Infection	191 (23)	220 (27)	231 (28)
	Pain	134 (16)	159 (20)	173 (21)
	Headache	90 (11)	99 (12)	108 (13)
	Injury, Accidental	58 (7)	72 (9)	85 (10)
	Flu Syndrome	59 (7)	70 (9)	72 (9)
	Pain, Back	43 (5)	57 (7)	64 (8)
	Asthenia	50 (6)	57 (7)	61 (7)
	Pain, Abdominal	47 (6)	53 (7)	59 (7)
	Pain, Chest	34 (4)	39 (5)	43 (5)
Cardiovascular	Flushing	513 (63)	525 (64)	528 (65)
Digestive	Nausea	83 (10)	98 (12)	100 (12)
	Diarrhea	82 (10)	89 (11)	94 (12)
	Dyspepsia	62 (8)	68 (9)	71 (9)
	Vomiting	36 (4)	51 (6)	57 (7)
	Flatulence	35 (4)	37 (5)	38 (5)
	Constipation	32 (4)	38 (5)	38 (5)
Metabolic and Nutritional	Hyperglycemia	45 (6)	50 (6)	53 (7)
	Edema, Peripheral	41 (5)	52 (6)	52 (6)
	CPK Increase	31 (4)	38 (5)	39 (5)
Musculoskeletal	Myalgia	31 (4)	37 (5)	41 (5)
Nervous	Dizziness	54 (7)	59 (7)	60 (7)
	Paresthesia	32 (4)	37 (5)	41 (5)
	Insomnia	33 (4)	38 (5)	38 (5)
Respiratory	Sinusitis	46 (6)	55 (7)	59 (7)
	Rhinitis	42 (5)	50 (6)	50 (6)
	Bronchitis	29 (4)	36 (4)	40 (5)
	Cough, Increased	33 (4)	36 (4)	39 (5)
Skin and Appendages	Pruritis	148 (18)	154 (19)	154 (19)
	Rash	96 (12)	105 (13)	108 (13)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. Four (4) additional patients reported myalgia since the Mar-2001 update (18-016, 25-010, 31-024, 35-011). None of these 4 patients required a change in their study medication due to the myalgias. There were no new cases of myopathy, rhabdomyolysis, or hepatitis reported.

b) Adverse Events Resulting in Study Drug Discontinuation

By the completion of the 48-week extension study, 32 of the 454 patients (4%) had discontinued due to an AE. The most commonly reported AE resulting in study drug discontinuation continued to be flushing; however, no new discontinuations due to flushing were reported since the Mar-2001 update. Only 2 additional patients discontinued study medication since the Mar-2001 update. The small number of new discontinuations is not unexpected as the patients continuing in the extension study had already demonstrated compliance and tolerance to study medication. The two new

discontinuations since the Mar-2001 update are: Patient 01-030 who discontinued due to nausea and vomiting; and Patient 26-020 who discontinued due to pruritus.

The most common AEs resulting in study drug discontinuation for the 48-week extension (Table 4) and the 52-week study (for comparison, Table 3) are as follows (A complete list of AEs resulting in study drug discontinuation for the extension study is in the Appendix)

Table 3: MA-07 52-Week Study Discontinuations Due to Adverse Events, Most Common

		52-Week Study
ITT Patients, n =		814
All Discontinuations, n (%)		264 (32)
Discontinued for AE*, n (%)		188 (23)
Body System	**COSTART Term**	n (%)
Body as a Whole	Headache	10 (1)
Cardiovascular	Flushing	79 (10)
Digestive	Diarrhea	12 (1)
	Nausea	11 (1)
Skin and Appendages	Pruritis	33 (4)
	Rash	20 (2)
Discontinued for Lab Abnormality		15 (2)

*Patients may have reported more than one AE term per discontinuation

Table 4: 48-Week Extension Study Discontinuations Due to Adverse Events, Mar-2001 & Sep-2001 Updates, Most Common (>1 Patient)

		Mar-2001	Sept-2001
Patients, n =		300	454
All Discontinuations, n (%)		47 (16)	57 (7)
Discontinued for AE*, n (%)		30 (10)	32 (4)
Body System	**COSTART Term**	n (%)	n (%)
Cardiovascular	Flushing	8 (3)	8 (3)
	Heart Arrest	2 (1)	2 (1)
Digestive	Nausea	4 (1)	5 (1)
	Vomiting	2 (1)	3 (1)
	Colitis	2 (1)	2 (1)
Metabolic and Nutritional	CPK increased	2 (1)	2 (1)
	Glucose tolerance decreased	2 (1)	2 (1)
Skin and Appendages	Pruritis	2 (1)	3 (1)
Discontinued for Lab Abnormality		3 (1)	3 (1)

*Patients may have reported more than one AE term per discontinuation

c) Serious Adverse Events

There were 16 additional SAEs in 13 patients reported in the Sept-2001 update. No new deaths were reported. The Cardiovascular system was most commonly affected (5 of the 16 SAEs, in 5 of 13 patients), followed by the Body as a Whole (4 events in 3 patients), Musculoskeletal (3 events in 3 patients), Digestive (2 events in 2 patients), and Nervous systems (2 events in 1 patient). No SAE was assessed by the Investigator as being related to study medication. Twelve (12) of the 13 patients who experienced an SAE were male, and 6 of the 13 patients were $\geq$65 years of age; however, as the number of SAEs was

small, no conclusions will be generated from this. The SAEs reported in the Sept-2001 safety update are listed in the following table

Table 5: 48-Week Extension Serious Adverse Events, Sept-2001 Update

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
02-014	M	65	Abdominal Pain	Dig	427	NR	N
02-038	M	50	Post-Traumatic Stress Disorder (PTSD)	Ner	469	NR	N
02-038	M	50	PSTD/Suicidal Ideation	Ner	609	NR	N
06-024	M	77	Coronary Occlusion	CV	476	NR	N
17-019	M	70	Left Leg Cellulitis	Body	707	NR	N
31-021	M	56	Congestive Heart Failure	CV	371	NR	N
35-012	M	53	Chest Pain, Non-Cardiac	Body	539	NR	N
35-013	M	67	Increased Angina	CV	658	NR	N
38-031	M	64	Hemorrhagic, Gangrenous Cholecystitis	Dig	504	NR	N
38-031	M	64	Subhepatic Abscess	Body	518	NR	N
38-031	M	64	Recurrent Subhepatic Abscess	Body	560	NR	N
39-005	M	56	Ruptured Quadriceps Tendon	MS	553	NR	N
42-003	F	81	Arthritis, Left Knee	MS	518	NR	N
45-001	M	56	Right Shoulder Pain, Rotator Cuff Tear	MS	Completed	NR	N (completed)
45-003	M	60	Ventricular Fibrillation	CV	378	NR	N
45-008	M	67	Coronary Occlusion	CV	658	NR	N

d) Other Significant Adverse Events

Two (2) additional patients were diagnosed with cancer during the extension study. These patients are:

Table 6: 48-Week Extension Other Significant Adverse Events

Patient	M/F	Age (yrs)	Diagnosis	Onset (days)	Investigator Attribution	Drug Discontinued?
11-034	M	69	Prostate Cancer	700	NR	N
12-015	M	51	Basal Cell (Skin) Cancer	679	NR	N

e) Treatment Emergent Laboratory Abnormalities

(1) ALT and AST

The incidence rates of ALT and AST elevations >normal were somewhat lower in the Sept-2001 update than in the 52-week study (6% vs 12% respectively), and AST and ALT elevations >2 X ULN were uncommon in both groups. There were no new cases of AST or ALT elevations >3 X ULN reported in the Sept-2001 update, and no patient was discontinued from the extension study due to an elevated AST or ALT. The incidence rates of ALT and AST elevations at the Jan-2001, Mar-2001, and Sept-2001 safety updates are as follows

Table 7: MA-07 Incidence of Treatment Emergent ALT and AST Elevations, Jan-2001, Mar-2001, and Sept-2001 Updates

	Jan-2001	Mar-2001	Sept-2001
Patients, n =	814	814	450
ALT >normal, n (%)	92 (11)	101 (12)	28 (6)
ALT >2 X ULN, n (%)	13 (2)	16 (2)	4 (1)
ALT >3 X ULN, n (%)	4 (<1)	4 (<1)	0
AST >normal, n (%)	75 (9)	83 (10)	20 (4)
AST >2 X ULN, n (%)	18 (2)	18 (2)	0
AST >3 X ULN, n (%)	5 (1)	5 (1)	0

ALT normal range: 6-53 IU/L
AST normal range: 3-34 IU/L

(2) Fasting Blood Sugar (FBS)

Mild elevations of FBS continued to be common in the 48-week extension study, as they were in the 52-week study. Fifty-five percent (55%) of patients in the extension study had at least one FBS >normal, compared to 67% of patients in the 52-week study. No new reports of patient discontinuations for FBS or HgA1C elevations were reported in the Sept-2001 safety update. The incidence of treatment emergent FBS elevations at the Jan-2001, Mar-2001, and Sept-2001 updates are as follows

Table 8: MA-07 Incidence of Treatment Emergent FBS Elevations, Jan-2001, Mar-2001, and Sept-2001 Updates

	Jan-2001	Mar-2001	Sept-2001
Patients, n =	814	814	450
FBS > normal	525 (64)	543 (67)	248 (55)
FBS >1.3 X ULN	165 (20)	171(21)	60 (13)
FBS >2 X ULN	33 (4)	36 (4)	7 (2)
FBS >3 X ULN	6 (1)	7(1)	1 (<1)

FBS >normal: >111 mg/dL, FBS >1.3 X ULN: >145 mg/dL,
FBS >2 X ULN: >221 mg/dL, FBS >3 X ULN: >330 mg/dL

Seven (7) patients experienced an FBS elevation >2 X ULN reported throughout the MA-07 extension study. One (1) patient (23-006) had an FBS > 3 X ULN resulting in early termination from the study, which was reported previously (in the NDA review dated 22-Jul-2001). The other patients completed the extension study. All FBS elevations >2 X ULN occurring in the extension study are summarized as follows:

Table 9: Extension Study Treatment Emergent Elevations FBS >2 X ULN

Patient	Week	FBS	Elevation
02-009	64	227	>2 X ULN
	76	231	>2 X ULN
	88	220	>2 X ULN
	100	234	>2 X ULN
02-026	64	261	>2 X ULN
	64 retest	178	>1.3 X ULN
	76	164	>1.3 X ULN
	88	148	>1.3 X ULN
	100	182	>1.3 X ULN
03-015	64	214	>1.3 X ULN
	64 retest	248	>2 X ULN
	76	242	>2 X ULN
	88	180	>1.3 X ULN
	100	180	>1.3 X ULN
12-006	64	226	>2 X ULN
	76	173	>1.3 X ULN
	88	216	>1.3 X ULN
	100	202	>1.3 X ULN
22-011	64	238	>2 X ULN
	76	87	
	88	89	
	88 retest	108	
	100	102	
	100 retest	124	
23-006	64	328	>3 X ULN
	ET	308	>2 X ULN
25-009	64	182	>1.3 X ULN
	76	238	>2 X ULN
	88	200	>1.3 X ULN
	100	255	>2 X ULN

(3) Phosphorous

Mild to moderate decreases in serum phosphorous continued to be common during the extension study, with 20% of patients experiencing at least one phosphorous level <normal during the extension study vs 29% in the 52-week study. Phosphorous decreases <2 X ULN were uncommon in the both groups. There were no clinically significant findings and no discontinuations due to low phosphorous in the extension study. The incidence of phosphorous decreases at the Jan-2001, Mar-2001, and Sept-2001 updates are as follows

Table 10: MA-07 Incidence of Treatment Emergent Phosphorous Decreases, Jan-2001, Mar-2001, and Sept-2001 Updates

	Jan-2001	**Mar-2001**	**Sept-2001**
Patients, n =	814	814	450
Phosphorous <normal	212 (26)	234 (29)	89 (20)
Phosphorous <2 X LLN	19 (2)	21 (3)	4 (1)

Phosphorous normal range: 2.4-4.3 mg/dL

(4) CPK

Mild elevations in CPK continued to be common during the extension study, with approximately 50% of patients in both groups experiencing any elevation in CPK value >normal. Two (2) patients (27-009) in the Sept-2001 update were reported as having experienced a CPK elevation >10 X ULN. The incidence of CPK elevations at the Jan-2001, Mar-2001, and Sept-2001 updates are as follows

Table 11: MA-07 Incidence of Treatment Emergent CPK Elevations, Jan-2001, Mar-2001 and Sept-2001 Updates

	Jan-2001	Mar-2001	Sept-2001
Patients, n =	814	814	450
CPK >normal	411 (50)	447 (55)	226 (50)
CPK > 5 X ULN	10 (1)	14 (2)	7 (2)
CPK > 10 X ULN	4 (<1)	5 (1)	2 (<1)

CPK upper limit of normal: Female 164 U/L, Male 207 U/L

The 2 patients (27-009 and 30-004) with clinically significant (>10 X ULN) CPK elevation are summarized in the following table

Table 12: 48-Week Extension Study Patients With Clinically Significant CPK Elevations, Sept-2001 Update

Week	CPK	Elevation	Dose	Contributing history
Patient 27-009				50 year old male. At Week 64, patient had CPK elevation felt to be secondary to exercise. Elevations resolved at follow-up. The patient discontinued study medication at approx. Week 73 due to military service, and failed to show for Week 88 visit. The patient was non-compliant with study medication and procedures, and was discontinued at approximately Week 88.
Baseline	151		None	
Week 64	6940	>10 X ULN	2000/40 X 53 weeks	
Week 64 retest	117		2000/40 X 55 weeks	
Week 76	174		2000/40 X 64 weeks	
ET	106		Off drug X 15 weeks	
Patient 30-004				43 year old male. Asymptomatic at the time of CPK elevation.
Baseline			None	
Week 64	1155	>5 X ULN		
Week 64 retest	169			
Week 76	566	>3 X ULN		
Week 88	2340	>10 X ULN		
Week 100	557	>normal		

(a) Other Laboratory Values

Ten patients experienced an amylase elevation >2 X ULN during the extension study. No patient was reported as being symptomatic, and all patients completed the study. One patient (17-032) experienced an amylase elevation >2 X ULN which included a narrative in the Sept-2001 update. This patient was a 51 year old asymptomatic male, who underwent amylase isoenzyme testing that was 100% pancreatic. The elevation resolved on retesting. The 10 patients with amylase elevations >2 X ULN at anytime during the extension study are summarized as follows

Table 13: Extension Study Treatment Emergent Amylase Elevation >2 X ULN

Patient	Week	Amylase	Elevation
03-011	64	367	>3 X ULN
	76	367	>3 X ULN
	76 retest	358	>3 X ULN
	88	377	>3 X ULN
	100	350	>3 X ULN
	100 retest	365	>3 X ULN
03-013	64	64	
	76	208	>2 X ULN
	88	226	>2 X ULN
	100	73	
11-030	64	181	>1.3 X ULN
	76	155	>1.3 X ULN
	88	152	>1.3 X ULN
	100	201	>2 X ULN
14-013	64	186	>1.3 X ULN
	76	148	>1.3 X ULN
	88	269	>2 X ULN
	100	99	
17-032	64	216	>2 X ULN
	64 retest	282	>2 X ULN
	64 retest	72	
	76	64	
	88	75	
	100	83	
18-010	64	64	
	76	196	>1.3 X ULN
	88	422	>3 X ULN
	88 retest	114	>normal
	100	73	
18-017	64	157	>1.3 X ULN
	76	146	>1.3 X ULN
	88	159	>1.3 X ULN
	100	206	>2 X ULN
31-021	52	218	>2 X ULN
	64	247	>2 X ULN
	64 retest	194	>1.3 X ULN
	76	221	>2 X ULN
	88	201	>2 X ULN
	100	210	>2 X ULN
38-005	64	85	
	76	91	
	88	139	>1.3 X ULN
	100	293	>2 X ULN
	100 retest	89	
38-007	64	78	
	76	58	
	88	66	
	100	235	>2 X ULN
	100 retest	70	

Four (4) patients were reported as experiencing a platelet count <100,000 at anytime during the extension study (Patients 07-015, 18-017, 30-008, 35-016). Patients 07-015, 18-017, and 30-008 were previously reported. Patients 35-016, a 51 year old male, had no symptoms reported referable to the low platelets. This patient completed the study. The platelet results are summarized in the following table

Table 14: Extension Study Treatment Emergent Platelet Count <100,000, Sept-2001 Update

Patient	Week	Platelet Count
35-016	64	76,000
	64 retest	101,000
	76	125,000
	88	87,000
	100	99,000

There were no other notable laboratory abnormalities reported during the extension study.

f) Overall Safety Conclusions for the MA-07 48-Week Extension Study

The safety results for the extension study were similar to the results for the original 52 weeks of the study. The types and frequencies of AEs were similar. Flushing continued to be the most commonly reported AE, followed by infection, pain, pruritus, rash, headache, nausea, and diarrhea. Seven percent (7%) of patients discontinued prior to study completion, most commonly due to AEs. Mild elevations in AST, ALT, CPK, and FBS, and mild decreases in phosphorous continued to be common in the extension study, as they were in the 52-week study; however, clinically significant laboratory abnormalities were uncommon in either the 52-week study or the extension study. Serious Adverse Events occurred in 13 additional patients (16 events). The majority of these SAEs were cardiovascular events, which is not unexpected in this group of patients.

B. Protocol MA-99-010409

1. Study Design for MA-09

a) Study Design

MA-98-010409 (MA-09) "Evaluation of the Safety and Efficacy of Advicor (a combination tablet of niacin extended-release/lovastatin immediate-release): An Open-Label Extension Study" was a 48-week, open-label, single-arm safety and efficacy extension study to the double-blind, controlled studies MA-14 and MA-06. MA-09 was similar in design to MA-07, and enrolled 240 patients who had previously completed either of the double-blind, controlled studies (MA-06 and MA-14).

b) Study Medication

As patients entering MA-09 from the MA-14 and MA-06 studies could have been on several different doses of Advicor, Niaspan, or lovastatin, all patients enrolled into the MA-09 extension study were started on an Advicor dose of 500/20 once daily at bedtime for 4 weeks, and forced dose-titrated every 4 weeks as follows

Table 15: MA-09 Dose Titration Schedule

	Week				
	0-4	**5-8**	**9-12**	**13-16**	**17-48**
Advicor dose (mg/mg)	500/20	1000/40	1500/40	2000/40	2000/40
Tablet strength	500/20	500/20	750/20	1000/20	1000/20
Number of tablets	1	2	2	2	2

The investigator could adjust the patient's study medication to a lower dose for patient tolerability and safety. There was no comparator arm in this study, and all patients received Advicor.

2. Results

Two hundred forty (240) patients were enrolled in the MA-09 study between 24-Mar-1999 and 19-Aug-1999. Patients who had completed MA-14 and MA-06 were offered enrollment in MA-09, so the patient eligibility criteria for MA-09 were similar to those for MA-14 and MA-06. As the MA-06 and MA-14 studies included treatment arms for Advicor, Niaspan alone, or lovastatin alone, patients entering MA-09 were either previously exposed to Advicor or were Advicor naïve. One hundred twenty-three (123) patients who were previously exposed to Advicor, and 117 patients who were Advicor-naïve were enrolled in the MA-09 study.

a) Baseline Demographics

Sixty (60%) of the patients who entered MA-09 were male, and 89% were Caucasian. Patients ranged in age from 28-78 years, with a mean age of 58.6. Demographic data are summarized in the following table (demographic data from the Mar-2001 interim report are included for comparison purposes)

Table 16: MA-09 Baseline Demographics

	Mar-2001 Update	Sept-2001 Update
Patients, n =	106	240
Demographic Measure		
Gender, n (%)		
Male	59 (56)	145 (60)
Female	47 (44)	95 (40)
Age, years		
mean	58.3	58.6
median	58.5	59
min, max	28, 78	28, 84
Age ≥ 65 years, n (%)	35 (33)	85 (35)
Ethnicity, n(%)		
Caucasian	98 (92)	214 (89)
Black	6 (6)	15 (6)
Hispanic	1 (1)	6 (3)
Other	1 (1)	5 (2)
Mean BMI, kg/M^2	29.0	29.1

b) Patient Disposition

The mean duration of study drug exposure for the 240 patients who continued in the MA-09 extension study was 43.9 weeks. One hundred ninety-five (195) patients completed the study, and 45 of the 240 patients (19%) withdrew from the study prior to completion. Thirty-two (32) of the 45 discontinuations were due to AEs. The reasons for patient discontinuations are summarized in the following table (Mar-2001 update results are included for comparison purposes)

Table 17: MA-09 Patients Discontinued Mar-2001 and Sept-2001 Updates

	Mar-2001 Update	Sept-2001 Update
Patients, n =	106	240
Number of Withdrawals, n (%)	38 (36)	45 (19)
Reason for Dropout, n (%)		
Adverse Event	30 (28)	32 (13)
Withdrew Consent	2 (2)	3 (1)
Lost to Follow Up	2 (2)	4 (2)
Other	4 (4)	6 (3)

The baseline demographics for the patients who dropped out were notable for relatively more female patients dropped out compared to all entered patients (49% females dropped out vs 40% of patients overall). Otherwise, there were no substantial differences between enrolled patients and dropouts. As the number of dropouts was relatively small (19% of all enrolled patients), it is unlikely that dropouts substantially affected the overall study results.

Baseline demographics of patients overall vs dropouts is summarized in the following table

Table 18: MA-09 Baseline Demographics of Patients Overall vs Dropouts

	Patients Overall	Dropouts
Patients, n =	240	45
Demographic Measure		
Gender, n (%)		
Male	145 (60)	23 (51)
Female	95 (40)	22 (49)
Age, years		
Mean	58.6	58.2
Median	59.0	59
min, max	28, 84	28,78
Age ≥ 65 years, n (%)	85 (35)	12 (27)
Ethnicity, n(%)		
Caucasian	214 (89)	40 (89)
Black	15 (6)	4 (9)
Hispanic	6 (3)	1 (2)
Other	5 (2)	0
Mean BMI, kg/M^2	29.1	28.8

3. Efficacy Results

No efficacy results were included in this update.

4. Safety Results

This safety update includes the final safety information on the 240 patients who completed the MA-09 study.

a) Adverse Events

There were 213 different AE terms reported by 186 of the 240 patients (78%) at any time during the study. Male vs female, and geriatric vs non-geriatric patients were about as likely to complain of any AE. Adverse Event incidence rates overall and by subgroup are as follows

Table 19: MA-09 Incidence of Adverse Events, Overall and by Subgroup

		Subgroup			
	All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	240	145	95	85	155
Patients Reporting Any AE, n (%)	186 (78)	114* (79)	71* (75)	62* (73)	123* (79)

*One patient (0411) sex and age unknown

b) Adverse Events by Body System

Adverse Events reported in the Sept-2001 update are similar to those reported in the interim report of Mar-2001. Flushing continued to be the most commonly reported AE, reported by 32% of patients at anytime during the study. Other frequently reported AEs were infection (17%), pain (14%), pruritus and accidental injury (9% each), and diarrhea (8%). The types of AEs reported in the MA-09 study are also similar to the AEs reported in other Advicor studies; however, the percentage of patients reporting flushing was

lower than for the other studies previously reported to this NDA. This may be due to many of the patients having been exposed to niacin previously in the MA-06 or MA-14 studies. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table (Mar-2001 data are presented for comparison purposes) [A list of common (≥2%) AEs is in the Appendix]

Table 20: MA-09 Most Common (≥5%) AEs at Mar-2001 and Sept-2001 Updates

		Mar-2001	Sept-2001
Patients, n =		106	240
Body System	**COSTART Term**	n (%)	n (%)
Body as a Whole	Infection	18 (17)	41 (17)
	Pain	10 (9)	34 (14)
	Injury, accidental	10 (9)	21 (9)
	Pain, abdominal	8 (8)	15 (6)
	Flu syndrome	10 (9)	13 (5)
	Pain, back	4 (4)	13 (5)
	Headache	6 (6)	11 (5)
Cardiovascular	Flushing	42 (40)	77 (32)
Digestive	Diarrhea	11 (10)	19 (8)
	Dyspepsia	9 (8)	14 (6)
	Nausea	9 (8)	14 (6)
Metabolic and Nutritional	Hyperglycemia	5 (5)	13 (5)
Respiratory	Rhinitis	5 (5)	12 (5)
	Sinusitis	6 (6)	11 (5)
Skin and Appendages	Pruritis	11 (10)	21 (9)
	Rash	8 (8)	13 (5)

Adverse Events of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. There were no reports of myopathy, rhabdomyolysis, or hepatitis. Myalgia was reported by 5 patients (0107, 0405, 2413, 0410, and 1417), one of whom (2413) was discontinued from the study (this was previously discussed in the July-2001 NDA review and will not be further discussed here). One of the remaining 4 patients (Patient 1417) had one CPK >normal, but none of the 4 patients had a CPK >2 X ULN.

c) Adverse Events by Subgroup

Adverse Events were further analyzed by subgroups. Females were more likely than males to complain of flushing (39% vs 28% respectively), nausea (11% vs 2%), and pruritus (13% vs 6%). Geriatric patients were more likely than non-geriatric patients to complain of pruritus (13% vs 6%). Non-geriatric patients were more likely than geriatric patients to complain of flu syndrome (8% vs 1%). As the number of patients in each subgroup was small, no definite conclusions will be drawn from this. There were no other notable differences between the subgroups. The most common (≥5%) AEs overall and by subgroup are summarized as follows

Table 21: MA-09 Incidence of Most Common (≥5%) Adverse Events Incidence, Overall and by Subgroup

			Subgroup			
		All	Male	Female	Geriatric	Non-Geriatric
Patients, n =		240	145	95	85	155
Body System	**COSTART Term**					
Body as a Whole	Infection	41 (17)	24 (17)	17 (18)	16 (19)	25 (16)
	Pain	34 (14)	17 (12)	16 (17)	14 (16)	19 (12)
	Injury, accidental	21 (9)	9 (6)	12 (13)	9 (11)	12 (8)
	Pain, abdominal	15 (6)	7 (5)	8 (8)	8 (9)	7 (5)
	Flu syndrome	13 (5)	9 (6)	4 (4)	1 (1)	12 (8)
	Pain, back	13 (5)	6 (4)	7 (7)	6 (7)	7 (5)
	Headache	11 (5)	8 (6)	3 (3)	2 (2)	10 (6)
Cardiovascular	Flushing	77 (32)	40 (28)	37 (39)	25 (29)	52 (34)
Digestive	Diarrhea	19 (8)	10 (7)	9 (9)	9 (11)	10 (6)
	Dyspepsia	14 (6)	9 (6)	5 (5)	3 (4)	11 (7)
	Nausea	14 (6)	3 (2)	10 (11)	7 (8)	6 (4)
Metabolic and Nutritional	Hyperglycemia	13 (5)	9 (6)	3 (3)	2 (2)	10 (6)
Respiratory	Rhinitis	12 (5)	8 (6)	4 (4)	2 (2)	10 (6)
	Sinusitis	11 (5)	9 (6)	2 (2)	2 (2)	9 (6)
Skin and Appendages	Pruritis	21 (9)	9 (6)	12 (13)	11 (13)	10 (6)
	Rash	13 (5)	8 (6)	5 (5)	4 (5)	9 (6)

d) Adverse Events Resulting in Drug Discontinuation

By the completion of the MA-09 study, 32 of the 240 patients (13%) had discontinued study medication prior to study completion due to Adverse Events. The most commonly reported AE resulting in study drug discontinuation was flushing (5% of patients). Two (2) additional patients discontinued study drug prior to study completion due to an AE since the Mar-2001 update. These patients (1017 and 2411) both discontinued secondary to flushing.

Discontinuations due to AEs were also analyzed by subgroup. Female patients were somewhat more likely than male patients to discontinue for any reason (23% vs 16% respectively), and for an AE (18% vs 10%). Female patients were also more likely than males to discontinue for flushing (8% vs 3%). Non-geriatric patients were somewhat more likely than geriatric patients to discontinue from the study for any reason (23% vs 14%), but were about equally as likely to discontinue for an AE (14% vs 13%). Geriatric patients were more likely to discontinue for flushing than non-geriatric patients (8% vs 3%). As the number of events per subgroup was small, no definite conclusions will be drawn from this. There were no other notable differences between the subgroups. The most common (≥5%) reasons for discontinuation due to AEs overall and by subgroup are summarized in the following table (A complete list of discontinuations due to AEs is listed in the Appendix).

Table 22: MA-09 Discontinuations Due to Adverse Events, Most Common Overall and by Subgroup

			Subgroup			
		All	Male	Female	Geriatric	Non-Geriatric
Patients, n =		240	145	95	85	155
All Discontinuations, n (%)		45 (19)	23 (16)	22 (23)	12 (14)	33 (23)
Discontinued for AE*, n (%)		32 (13)	15 (10)	17 (18)	11 (13)	21 (14)
Body System	**COSTART Term**	n (%)				
Cardiovascular	Flushing	12 (5)	4 (3)	8 (8)	7 (8)	5 (3)
Digestive	Diarrhea	3 (1)	2 (1)	1 (1)	0	3 (2)
	Dyspepsia	3 (1)	1 (1)	2 (2)	1 (1)	2 (1)
Metabolic and Nutritional	CPK increase	5 (2)	3 (2)	2 (2)	1 (1)	4 (3)
	Hyperuricemia	2 (1)	1 (1)	1 (1)	0	2 (1)
	Hyperglycemia	2 (1)	0	2 (2)	1 (1)	1 (1)
Skin and Appendages	Pruritis	3 (1)	1 (1)	2 (2)	1 (1)	2 (1)

*Patients may have reported more than one AE term per discontinuation

e) Serious Adverse Events

There were 13 Serious Adverse Events (SAEs) occurring in 11 patients reported in the Sept-2001 safety update. There were no new deaths. Four (4) of the 13 SAEs occurred in the Body as a Whole body system, followed by the Cardiovascular and Digestive systems (3 each), Musculoskeletal system (2), and Respiratory system (1). Eight (8) of the 11 patients were male (accounting for 9 of 13 SAEs), and 5 of the 11 patients (accounting for 7 of 13 SAEs) were ≥65 years of age. The SAEs reported in the Sept-2001 safety update are listed in the following table

Table 23: MA-09 Serious Adverse Events, Sept-2001 Update

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
0305	M	61	Coronary Occlusion	CV	49	NR	N
0809	M	58	Right Colon Angiodysplasia/Rectal Bleeding	Dig	224	NR	Y
1014	M	63	Recurrent Ventral Hernia	Body	77	NR	N
1108	M	53	Chest Pain, Non-Cardiac	Body	77	NR	N
1308	M	60	Degenerative Disc Disease/Bilateral Neural Foraminal Stenosis	MS	266	NR	N
1309	F	67	CHF/Atrial Flutter	CV	105	NR	N
1314	M	34	Atypical Chest Pain	Body	266	NR	N
1601	F	71	Angina	CV	56	NR	N
1704	F	69	Right Tri-Malleolar Fracture	MS	238	NR	N
1707	M	70	Abdominal Pain/Sigmoid Volvulus	Dig	182	NR	N
1707	M	70	Post-Operative Infection	Body	182	NR	N
1707	M	70	Pneumonia	Resp	182	NR	N
2019	F	71	Abdominal Pain/Diverticulitis	Dig	343	NR	Y

f) Other Significant Adverse Events

Two (2) additional patients were reported as having been diagnosed with cancer since the Mar-2001 safety update. These patients are summarized in the following table

Table 24: MA-09 Other Significant Adverse Events, Sept-2001 Update

Patient	M/F	Age (yrs)	Diagnosis	Onset (days)	Investigator Attribution	Drug Discontinued?
0815	M	73	Prostate Cancer	98	NR	N
1104	M	45	Basal Cell (Skin) Cancer	98	NR	N

g) Treatment Emergent Laboratory Abnormalities

(1) ALT and AST

Mild elevations from baseline in ALT and AST were common, and occurred in 15% and 39% of patients respectively at any time during the study. One patient experienced an elevation in AST >3 X ULN during the study that resolved on retesting. No patient discontinued study drug due to an AST or ALT elevation. The incidence of treatment emergent ALT and AST elevations are summarized in the following table

Table 25: MA-09 Incidence of Treatment Emergent ALT and AST Elevations

	Mar-2001	Sept-2001
Patients, n =	106	240
ALT >normal, n (%)	16 (15)	35 (15)
ALT >2 X ULN, n (%)	0	0
ALT >3 X ULN, n (%)	0	0
AST >normal, n (%)	38 (36)	94 (39)
AST >2 X ULN, n (%)	1 (1)	4 (2)
AST >3 X ULN, n (%)	0	1 (<1)

The patient (2105) experiencing the AST elevation >3 X ULN is summarized as follows

Table 26: MA-09 Treatment Emergent AST Elevation >3 X ULN

Patient	Week	AST	Elevation	Contributing History
2105	Screening	39	>normal	63 year old female.
	Week 4	119	>3.0X ULN	Asymptomatic
	Week 4 retest	48	>normal	
	Week 12	46	>normal	
	Week 48	35	>normal	

(2) Fasting Blood Sugar

Mild elevations from baseline in FBS were common, and occurred in 46% of study patients at any time during the study. More severe FBS elevations were uncommon, however, with 3% of patients experiencing FBS elevations >2 X ULN at any time during the study. No new patients were reported as having been discontinued due to an elevated FBS, worsening HgA1C, or new diagnosis of diabetes in the Sept-2001 update. The incidence of treatment emergent FBS elevations are summarized in the following table

Table 27: MA-09 Incidence of Treatment Emergent FBS Elevations

	Mar-2001	Sept-2001
Patients, n =	106	240
FBS >normal, n (%)	50 (47)	111 (46)
FBS >1.3 X ULN, n (%)	11 (10)	36 (15)
FBS >2 X ULN, n (%)	1 (1)	6 (3)
FBS >3 X ULN, n (%)	0	0

Patients experiencing FBS elevations >2 X ULN during the study are summarized in the following table

Table 28: MA-09 Treatment Emergent FBS Elevations >2 X ULN

Patient	Week	FBS	Elevation	Contributing History
0210	Screening	169	>1.3X	52 year old male. Asymptomatic.
	Week 4	218	>1.3X	
	Week 8	247	>2.0X	
	Week 12	204	>1.3X	
	Week 24	190	>1.3X	
	Week 36	216	>1.3X	
	Week 48	179	>1.3X	
0706	Screening	178	>1.3X	51 year old male. Asymptomatic.
	Week 4	194	>1.3X	
	Week 8	251	>2.0X	
	Week 8 retest	207	>1.3X	
	Week 12	199	>1.3X	
	Week 24	195	>1.3X	
	Week 36	200	>1.3X	
	Week 48	182	>1.3X	
0801	Screening	182	>1.3X	70 year old male. Patient was noted to have increased serum and urine glucose, increased HgA1C, and nocturia
	Week 4	197	>1.3X	
	Week 8	210	>1.3X	
	Week 12	227	>2.0X	
	Week 24	207	>1.3X	
	Week 36	221	>2.0X	
	Week 48	282	>2.0X	
	Week 48 retest	239	>2.0X	
1906	Screening	186	>1.3X	55 year old male. Asymptomatic.
	Week 4	178	>1.3X	
	Week 8	224	>2.0X	
	Week 8 retest	196	>1.3X	
	Week 12	192	>1.3X	
	Week 24	163	>1.3X	
	Week 36	147	>1.3X	
	Week 48	168	>1.3X	

Table 28: MA-09 Treatment Emergent FBS Elevations >2 X ULN, cont.

Patient	Week	FBS	Elevation	Contributing History
0712	Week 4	125	>1.0X	38 year old female. Asymptomatic.
	Week 8	137	>1.0X	
	Week 12	226	>2.0X	
	Week 12 retest	179	>1.3X	
	Week 12 retest	124	>1.0X	
	Week 12 retest	125	>1.0X	
	Week 24	114	>1.0X	
1709	Screening	148	>1.3X	53 year old male. Asymptomatic.
	Week 4	163	>1.3X	
	Week 8	142	>1.0X	
	Week 12	171	>1.3X	
	Week 24	221	>2.0X	
	Week 36	165	>1.3X	
	Week 48	133	>1.0X	

(3) Phosphorous

Mild to moderate treatment emergent decreases in serum phosphorous were common, and occurred in 30% of patients. Serum phosphorous <normal was more common in males (37%) than females (21%). No clinically significant findings and no discontinuations were attributed to low serum phosphorous, and no clinically significant changes in serum calcium were noted. The clinical significance of mild to moderate hypophosphatemia in this group of patients is unknown. The incidences of phosphorous decreases are as follows

Table 29: MA-09 Incidence of Treatment Emergent Phosphorous Decreases

	Mar-2001	Sept-2001
Patients, n =	106	240
Phosphorous <normal, n (%)	27 (25)	73 (30)
Phosphorous <2 X ULN, n (%)	5 (5)	14 (6)

(4) CPK

Mild elevations in CPK occurred in 35% of patients, and were of no clinical importance. Two patients had CPK elevations >5 X ULN, and no patients with CPK elevations >10 X ULN were reported. No additional patients had study drug treatment discontinued due to CPK elevations reported in the Sept-2001 update. The incidence of CPK elevations is as follows

Table 30: MA-09 Incidence of Treatment Emergent CPK Elevations

	Mar-2001	Sept-2001
Patients, n =	106	240
CPK >normal, n (%)	37 (35)	83 (35)
CPK>5 X ULN, n (%)	1 (1)	2 (1)
CPK >10 X ULN, n (%)	0	0

(5) Other Laboratory Values

Two patients had platelet counts <100,000/mm^3 during the study. Both patients were asymptomatic and completed the study. These patients are summarized as follows

Table 31: MA-09 Treatment Emergent Platelet Counts <100,000/mm^3

Patient	Week	Platelet Count	Dose	Contributing History
1705	Baseline	224,000	None	52 year old male, without related symptoms. Platelet count at Weeks 24 and 48 felt to be unreliable due to clumping. The patient completed the study
	Week 24	Clotted - no result	2000/40 X 12 weeks	
	Week 48	61,000	2000/40 X 36 weeks	
	Week 48 retest	201,000	Off drug X 2 weeks	
1010	Baseline	113,000	None	73 year old male, asymptomatic
	Week 24	93,000		
	Week 24 retest	95,000		
	Week 48	94,000		

There were 2 additional patients reported in the Sept-2001 update with PT elevations >2 X ULN (Patients 0405 and 1309). Patient 1309 was receiving Coumadin. Neither had symptoms of bleeding, and both patients completed the study. These patients are summarized as follows

Table 32: MA-09 Treatment Emergent PT >2 X ULN, Sept-2001 Update

Patient	Week	PT	PTT	PT Elevation	Contributing History
0405	Screening	15.00	24.30	>1.0X	71 year old male. Asymptomatic.
0405	Week 24	36.10	32.00	>3.0X	
0405	Week 48	33.90	36.40	>3.0X	
1309	Screening	23.40	31.50	>1.3X	66 year old female. Symptomatic, on Coumadin.
1309	Week 24	35.20	31.40	>3.0X	
1309	Week 48	ND	ND		

There were no other notable laboratory abnormalities during the MA-09 study.

h) Overall Safety Conclusions for Protocol MA-09

The safety results for MA-09 were similar to those for the other clinical studies submitted to the NDA, and were similar to the MA-09 interim safety report submitted in Mar-2001. Adverse Events were reported by 78% of study patients at anytime during the study. Cardiovascular system AEs were the most commonly reported, almost all of which were complaints of flushing. Forty-five (45) of the 240 patients (19%) discontinued prior to study completion, with 32 patients (13%) discontinuing due to an AE. Flushing was the most commonly reported AE as the reason for discontinuation. Female patients were also

more likely than male patients to discontinue for any reason and due to an AE. Mild abnormalities in AST, ALT, FBS, CPK, and phosphorous were common, but clinically significant treatment emergent laboratory abnormalities were uncommon. Serious Adverse Events were reported in an additional 11 patients (13 events) since the Mar-2001 update.

C. Overall Safety Conclusions

The safety results reported in this 12-month safety update to NDA 21-249 are similar to the previously reported study safety results. There were no findings that would necessitate any change to the current labeling for Advicor.

D. Appendix

Table 33: MA-07 Common (≥2%) AEs at Jan-2001, Mar-2001, and Sept-2001 Updates

Patients, n =		Jan-2001 Update 814	Mar-2001 Update 814	Sept-2001 Update 814
Body System	**COSTART Term**			
Body as a Whole	Infection	191 (23)	220 (27)	231 (28)
	Pain	134 (16)	159 (20)	173 (21)
	Headache	90 (11)	99 (12)	108 (13)
	Injury, Accidental	58 (7)	72 (9)	85 (10)
	Flu Syndrome	59 (7)	70 (9)	72 (9)
	Pain, Back	43 (5)	57 (7)	64 (8)
	Asthenia	50 (6)	57 (7)	61 (7)
	Pain, Abdominal	47 (6)	53 (7)	59 (7)
	Pain, Chest	34 (4)	39 (5)	43 (5)
	Allergic Reaction	17 (2)	25 (3)	29 (4)
	Fever	17 (2)	19 (2)	22 (3)
	Pain, Neck	15 (2)	19 (2)	21 (3)
	Infection, fungal	10 (1)	17 (2)	21 (3)
	Hernia	8 (1)	11 (1)	17 (2)
	Infection, Viral	8 (1)	12 (1)	13 (2)
Cardiovascular	Flushing	513 (63)	525 (64)	528 (65)
	Hypertension	20 (2)	30 (4)	36 (4)
	Angina Pectoris	17 (2)	19 (2)	21 (3)
	Cardiovascular Disorder	18 (2)	24 (3)	26 (3)
	Palpitations	15 (2)	17 (2)	18 (2)
	Vascular Disorder	8 (1)	15 (2)	18 (2)
	Occlusion, Coronary	9 (1)	12 (1)	14 (2)
	Hematoma	10 (1)	11 (1)	13 (2)
Digestive	Nausea	83 (10)	98 (12)	100 (12)
	Diarrhea	82 (10)	89 (11)	94 (12)
	Dyspepsia	62 (8)	68 (9)	71 (9)
	Vomiting	36 (4)	51 (6)	57 (7)
	Constipation	32 (4)	38 (5)	38 (6)
	Flatulence	35 (4)	37 (5)	38 (5)
	Gastrointestinal Disorder	20 (2)	26 (3)	29 (3)
	Colitis	10 (1)	15 (2)	17 (2)
	Abscess, Periodontal	14 (2)	16 (2)	16 (2)
	Anorexia	9 (1)	12 (1)	13 (2)
Hematologic and Lymphatic	Ecchymosis	23 (3)	25 (3)	27 (3)
	Anemia	12 (1)	18 (2)	18 (2)
Metabolic and Nutritional	Hyperglycemia	45 (6)	50 (6)	53 (7)
	Edema, Peripheral	41 (5)	52 (6)	52 (6)
	CPK Increase	31 (4)	38 (5)	39 (5)
	Glucose Tolerance Decrease	22 (3)	26 (3)	27 (3)
	Diabetes Mellitus	17 (2)	20 (2)	22 (3)
	Hypokalemia	11 (1)	13 (2)	14 (2)
Musculoskeletal	Myalgia	31 (4)	37 (5)	41 (5)
	Cramps, Leg	24 (3)	28 (3)	29 (3)
	Arthritis	13 (2)	19 (2)	26 (3)
	Bone Disorder	9 (1)	16 (2)	18 (2)
	Tendon Disorder	13 (2)	15 (2)	15 (2)
	Arthralgia	9 (1)	10 (1)	15 (2)
Nervous	Dizziness	54 (7)	59 (7)	60 (7)
	Paresthesia	32 (4)	37 (5)	41 (5)
	Insomnia	33 (4)	38 (5)	38 (6)
	Depression	20 (2)	21 (3)	25 (3)
	Anxiety	17 (2)	18 (2)	23 (3)
	Dry Mouth	18 (2)	19 (2)	22 (3)

Table 33: MA-07 Common (≥2%) AEs at Jan-2001, Mar-2001, and Sept-2001 Updates

Patients, n =		Jan-2001 Update 814	Mar-2001 Update 814	Sept-2001 Update 814
Body System	**COSTART Term**			
Nervous cont.	Hypertonia	11 (1)	13 (2)	15 (2)
Respiratory	Sinusitis	46 (6)	55 (7)	59 (7)
	Rhinitis	42 (5)	50 (6)	50 (6)
	Bronchitis	29 (4)	36 (4)	40 (5)
	Cough, Increase	33 (4)	36 (4)	39 (5)
	Pharyngitis	23 (3)	29 (4)	29 (4)
	Dyspnea	14 (2)	21 (3)	24 (3)
	Pneumonia	12 (1)	15 (2)	15 (2)
Skin and	Pruritis	148 (18)	154 (19)	154 (19)
Appendages	Rash	96 (12)	105 (13)	108 (13)
	Skin, Dry	21 (3)	24 (3)	24 (3)
	Sweating	15 (2)	15 (2)	16 (2)
	Herpes Zoster	8 (1)	11 (1)	13 (2)
Special Senses	Cataract	7 (1)	12 (1)	13 (2)
	Conjunctivitis	11 (1)	11 (1)	13 (2)
Urogenital	Infection, Urinary Tract	19 (2)	25 (3)	27 (3)
	Prostate disorder	8 (1)	14 (2)	16 (2)

Table 34: MA-09 Common (≥2%) AEs at Mar-2001 and Sept-2001 Updates

		Mar-2001	Sept-2001
Patients, n =		106	240
Body System	**COSTART Term**	n (%)	n (%)
Body as a Whole	Infection	18 (17)	41 (17)
	Pain	10 (9)	34 (14)
	Injury, accidental	10 (9)	21 (9)
	Pain, abdominal	8 (8)	15 (6)
	Flu syndrome	10 (9)	13 (5)
	Pain, back	4 (4)	13 (5)
	Headache	6 (6)	11 (5)
	Asthenia	4 (4)	10 (4)
	Pain, chest	3 (3)	10 (4)
	Pain, neck	0	7 (3)
	Cellulitis	1 (1)	5 (2)
	Infection, viral	1 (1)	4 (2)
	Infection, fungal	2 (2)	4 (2)
	Allergic reaction	3 (3)	3 (1)
Cardiovascular	Flushing	42 (40)	77 (32)
	Hypertension	4 (4)	7 (3)
	Cardiovascular disorder	4 (4)	5 (2)
	Angina Pectoris	1 (1)	5 (2)
	Vascular disorder	2 (2)	4 (2)
	Coronary artery disorder	2 (2)	2 (1)
	Vein, varicose	2 (2)	2 (1)
Digestive	Diarrhea	11 (10)	19 (8)
	Dyspepsia	9 (8)	14 (6)
	Nausea	9 (8)	14 (6)
	GI disorder	6 (6)	9 (4)
	Flatulence	5 (5)	8 (3)
	Vomiting	4 (4)	8 (3)
	Abscess, periodontal	3 (3)	6 (3)
	Constipation	0	5 (2)
	Ulcer, mouth	2 (2)	2 (1)
Hematologic and Lymphatic	Anemia	2 (2)	6 (3)
	Ecchymosis	2 (2)	4 (2)
	RBC abnormality	2 (2)	2 (1)
Metabolic and Nutritional	Hyperglycemia	5 (5)	13 (5)
	Edema, peripheral	4 (4)	9 (4)
	CPK, increased	5 (5)	8 (3)
	Glucose tolerance, decreased	2 (2)	5 (2)
	SGOT, increased	2 (2)	4 (2)
	Hyperuricemia	2 (2)	3 (1)
	Creatinine, increased	2 (2)	2 (1)
	Edema	2 (2)	2 (1)
Musculoskeletal	Arthritis	4 (4)	9 (4)
	Tendon disorder	2 (2)	9 (4)
	Cramps, leg	4 (4)	7 (3)
	Myalgia	2 (2)	5 (2)
	Bursitis	1 (1)	5 (2)
	Bone Disorder	0	5 (2)
	Arthralgia	3 (3)	4 (2)
	Joint disorder	2 (2)	3 (1)
Nervous	Anxiety	4 (4)	10 (4)

Table 34: MA-09 Common (≥2%) AEs at Mar-2001 and Sept-2001 Updates

		Mar-2001	Sept-2001
Patients, n =		106	240
Body System	**COSTART Term**	n (%)	n (%)
Nervous cont.	Insomnia	3 (3)	8 (3)
	Dizziness	2 (2)	6 (3)
	Depression	1 (1)	5 (2)
	Paresthesia	1 (1)	5 (2)
	Somnolence	0	4 (2)
	Dry mouth	2 (2)	2 (1)
	Hypertonia	2 (2)	2 (1)
	Hypesthesia	2 (2)	2 (1)
Respiratory	Rhinitis	5 (5)	12 (5)
	Sinusitis	6 (6)	11 (5)
	Bronchitis	4 (4)	9 (4)
	Cough Increased	0	7 (3)
	Pneumonia	0	4 (2)
	Dyspnea	2 (2)	3 (1)
	Lung disorder	2 (2)	2 (1)
Skin and	Pruritis	11 (10)	21 (9)
Appendages	Rash	8 (8)	13 (5)
	Skin, dry	6 (6)	8 (3)
	Dermatitis, fungal	2 (2)	2 (1)
	Hyperpigmentation	2 (2)	2 (1)
Special Senses	Ear disorder	2 (2)	2 (1)
	Glaucoma	2 (2)	3 (1)
Urogenital	Infection, urinary tract	3 (3)	9 (4)
	Urinary abnormality	2 (2)	7 (3)
	Prostate disorder	4 (4)	5 (2)
	Hematuria	2 (2)	5 (2)
	Albuminuria	0	5 (2)

APPEARS THIS WAY
ON ORIGINAL

Table 35: 48-Week Extension Study Discontinuations Due to Adverse Events, Mar-2001 & Sep-2001

		Mar-2001	Sept-2001
Patients, n =		300	454
All Discontinuations, n (%)		47 (16)	57 (7)
Discontinued for AE*, n (%)		30 (10)	32 (4)
Body System	**COSTART Term**	n (%)	n (%)
Body as a Whole	Allergic reaction	1 (<1)	1 (<1)
	Pain	1 (<1)	1 (<1)
	Pain, back	1 (<1)	1 (<1)
Cardiovascular	Flushing	8 (3)	8 (3)
	Heart Arrest	2 (1)	2 (1)
	Anomaly, vascular	1 (<1)	1 (<1)
	Cardiovascular disorder	1 (<1)	1 (<1)
	Hemorrhaging	1 (<1)	1 (<1)
	Infarction, myocardial	1 (<1)	1 (<1)
	Palpitations	1 (<1)	1 (<1)
Digestive	Nausea	4 (1)	5 (1)
	Vomiting	2 (1)	3 (1)
	Colitis	2 (1)	2 (1)
	Diarrhea	1 (<1)	1 (<1)
	Constipation	1 (<1)	1 (<1)
	Gastric hemorrhage	1 (<1)	1 (<1)
	GI disorder	1 (<1)	1 (<1)
	Hepatitis	1 (<1)	1 (<1)
	Rectal disorder	1 (<1)	1 (<1)
	Ulcer duodenal perforated	1 (<1)	1 (<1)
Metabolic and Nutritional	CPK increased	2 (1)	2 (1)
	Glucose tolerance decreased	2 (1)	2 (1)
	Hyperglycemia	1 (<1)	1 (<1)
Musculoskeletal	Cramps, leg	1 (<1)	1 (<1)
	Tendon disorder	1 (<1)	1 (<1)
Nervous	Nervousness	1 (<1)	1 (<1)
Respiratory	Dyspnea	1 (<1)	1 (<1)
Skin and Appendages	Pruritis	2 (1)	3 (1)
	Rash	1 (<1)	1 (<1)
	Dermatitis, fungal	1 (<1)	1 (<1)
Urogenital	Sexual function abnormality	1 (<1)	1 (<1)
Discontinued for Lab Abnormality		3 (1)	3 (1)

*Patients may have reported more than one AE term per discontinuation

Table 36: MA-09 Discontinuations Due to Adverse Events, Mar-2001 and Sept-2001 Updates

		Mar-2001	Sept-2001
Patients, n =		106	240
All Discontinuations, n (%)		38 (36)	45 (19)
Discontinued for AE*, n (%)		30 (28)	32 (13)
Body System	**COSTART Term**	n (%)	
Body as a Whole	Allergic reaction	1 (3)	1 (<1)
	Infection, bacterial	1 (3)	1 (<1)
	Pain, abdominal	1 (3)	1 (<1)
	Pain, chest	1 (3)	1 (<1)
Cardiovascular	Flushing	11 (37)	12 (5)
Digestive	Diarrhea	4 (13)	3 (1)
	Dyspepsia	4 (13)	3 (1)
	Flatulence	2 (7)	1 (<1)
	Appetite increase	1 (3)	1 (<1)
	GI disorder	1 (3)	1 (<1)
	Intestinal Perforation	0	1 (<1)
	Nausea	1 (3)	1 (<1)
	Stomatitis	1 (3)	1 (<1)
Hematologic and Lymphatic	Anemia, hypochromic	1 (3)	1 (<1)
	Anemia, macrocytic	1 (3)	1 (<1)
Metabolic and Nutritional	CPK increase	7 (23)	5 (2)
	Hyperuricemia	4 (13)	2 (1)
	Hyperglycemia	3 (10)	2 (1)
	SGOT increase	2 (7)	1 (<1)
	SGPT increase	2 (7)	1 (<1)
Musculoskeletal	Myalgia	2 (7)	1 (<1)
	Arthralgia	1 (3)	1 (<1)
	Osteomyelitis	1 (3)	1 (<1)
Nervous	Dry mouth	2 (7)	1 (<1)
Skin and Appendages	Pruritis	4 (13)	3 (1)
	Rash	3 (10)	1 (<1)
	Herpes zoster	1 (3)	1 (<1)
	Urticaria	1 (3)	1 (<1)
Discontinued for Lab abnormality		6 (6)	6 (3)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anne Pariser
10/19/01 07:42:38 AM
MEDICAL OFFICER

Mary Parks
10/24/01 12:43:01 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL