geriatric patients (3%). A complete list of SAEs occurring in the extension study is in Appendix VII.

### (4) Other Significant Adverse Events

Five (5) patients were diagnosed with cancer during the extension study. These patients are:

**Table 125: 48-Week Extension Study Other Significant Adverse Events**

| Patient | M/F | Age (yrs) | Diagnosis | Onset (days) | Investigator Attribution | Drug Discontinued? |
|---|---|---|---|---|---|---|
| 05-016 | F | 71 | Right breast cancer recurrence | 392 | NR | Y |
| 12-005 | F | 68 | Breast cancer/invasive ductal | 504 | NR | N |
| 20-004 | M | 72 | Lung cancer/adenocarcinoma | 714 | NR | N (completed) |
| 26-004 | M | 65 | Bladder cancer/transitional cell | 560 | NR | Y |
| 26-007 | F | 77 | Skin cancer/Basal cell | 588 | NR | N |

### (5) Treatment Emergent Laboratory Abnormalities

### (a) ALT and AST

Mild elevations in ALT and AST were common in the 48-week extension study as well as in the 52-week study. There were no new cases of AST or ALT elevations >3 X ULN, and no patient was discontinued from the extension study due to an elevated AST or ALT. The incidence of ALT and AST elevations at the Jan-2001 and Mar-2001 safety updates are as follows

**Table 126: MA-07 Incidence of Treatment Emergent ALT and AST Elevations, Jan-2001 and Mar-2001 Updates**

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

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

### (b) Fasting Blood Sugar

Mild elevations of FBS were common in the 48-week extension study as well as in the 52-week study. Two patients were discontinued from the extension study due to elevations in FBS or HgA1C. The incidence of treatment emergent FBS elevations at the Jan-2001 and Mar-2001 updates are as follows

**Table 127: MA-07 Incidence of Treatment Emergent FBS Elevations, Jan-2001 and Mar-2001 Updates**

| | Jan-2001 | Mar-2001 |
|---|---|---|
| Patients, n = | 814 | 814 |
| **FBS > normal** | 525 (64) | 543 (67) |
| **FBS >1.3 X ULN** | 165 (20) | 171(21) |
| **FBS >2 X ULN** | 33 (4) | 36(4) |
| **FBS >3 X ULN** | 6 (1) | 7(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

The two patients who discontinued during the extension study due to glucose abnormalities are summarized in the following table

**Table 128: 48-Week Extension Study Patients Discontinuing Due to FBS or HgA1C Abnormalities**

| Week | FBS | HgA1C | Dose | Contributing history |
|---|---|---|---|---|
| **Patient 22-016** | | | | |
| Baseline | 123 | 6.9 | None | 70 year old female, history of type 2 diabetes mellitus (DM). Patient was discontinued due to elevations in FBS and HgA1C. |
| Week 64 | 161 | 7.8 | 1500/40 X 13 weeks | |
| Week 64 retest | 146 | 7.9 | 1500/40 X 14 weeks | |
| Week 64 retest | 134 | 7.0 | Off study drug X 9 weeks | |
| ET | 131 | ND | Off study drug X 11 weeks | |
| **Patient 23-006** | | | | |
| Baseline | 195 | 8.9 | None | 62 year old male, history of type 2 DM. Patient was discontinued due to an elevated HgA1C. |
| Week 64 | 328 | 9.5 | 2000/40 X 51 weeks | |
| ET | 308 | 9.1 | Off study drug X 4 days | |
| ET retest | 204 | 8.3 | Off study drug X 7 weeks | |

### (c) Phosphorous

Mild to moderate decreases in serum phosphorous were also common during the extension study. 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 and Mar-2001 updates are as follows

**Table 129: MA-07 Incidence of Treatment Emergent Phosphorous Decreases, Jan-2001 and Mar-2001 Updates**

| | Jan-2001 | Mar-2001 |
|---|---|---|
| Patients, n = | 814 | 814 |
| **Phosphorous <normal** | 212 (26) | 234 (29) |
| **Phosphorous <2 X LLN** | 19 (2) | 21 (3) |

Phosphorous normal range: 2.4-4.3 mg/dL

### (d) CPK

Mild elevations in CPK were also common during the extension study. One patient (12-009) was discontinued due to an elevated CPK, and one patient (30-004) experienced a CPK elevation >10 X ULN during the study. The incidence of CPK elevations at the Jan-2001 and Mar-2001 updates are as follows

**Table 130: MA-07 Incidence of Treatment Emergent CPK Elevations, Jan-2001 and Mar-2001 Updates**

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

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

The two patients with clinically significant (>10 X ULN or resulting in discontinuation) CPK elevations are summarized in the following table

**Table 131: 48-Week Extension Study Patients With Clinically Significant CPK Elevations**

| Week | CPK | Elevation | Dose | Contributing history |
|---|---|---|---|---|
| **Patient 12-009** | | | | |
| Baseline | 137 | | None | 57 year old male. At Week 76 the patient exercised strenuously, and was asymptomatic. The patient was discontinued due to persistently elevated CPK. |
| Week 64 | 957 | >5 X ULN | 2000/40 X 53 weeks | |
| Week 64 retest | 455 | >normal | 2000/40 X 61 weeks | |
| Week 76 | 1320 | >5 X ULN | 2000/40 X 66 weeks | |
| Week 88 | 1380 | >5 X ULN | 2000/40 X 78 weeks | |
| Week 88 retest | 377 | >normal | Off study drug X 2 weeks | |
| ET | 564 | >3 X ULN | Off study drug X 4 weeks | |
| ET retest | 153 | | Off study drug X 13 weeks | |
| **Patient 30-004** | | | | |
| Baseline | 236 | >normal | None | 43 year old male. No contributing history provided. Patient completed the study. |
| Week 64 | 1155 | >5 X ULN | unknown | |
| Week 64 retest | 169 | | | |
| Week 76 | 566 | >3 X ULN | | |
| Week 88 | 2340 | >10 X ULN | | |
| Week 100 | 557 | >normal | | |

### (e) Other Laboratory Values

Three patients experienced amylase elevations >2 X ULN during the extension study, all of which resolved. All 3 patients were asymptomatic. Four (4) patients had PT elevations >2 X ULN (18-016, 32-003, 34-005, 32-016). No clinical sequelae were reported with these elevations. Treatment emergent platelet decreases <100,000 occurred in 3 patients. One patient (18-017) also experienced persistently decreased platelets during the 52-week study. The 3 patients are summarized in the following table

**Table 132: MA-07 Treatment Emergent Platelet Counts <100,000**

| Patient | Week | Platelet Count (X 1,000) | Contributing History |
|---|---|---|---|
| 07-015 | Baseline | 256 | 54 year old female, history of psueudothrombocytopenia due to platelet clumping. No contributing history. |
| | Week 76 | 58 | |
| | Week 88 | 88 | |
| | Week 100 | Not done | |
| 18-017 | Baseline | 153 | 75 year old male, history of thrombocytopenia. At Week 64 the patient was placed on [redacted] secondary to hematologic abnormalities. The hematologic abnormalities had not resolved by study completion (Week 100). Dose of Advicor was decreased from 2000/40 to 1000/20 at Week 52, and continued at 1000/20 until study completion. |
| | Week 16 | 110 | |
| | Week 28 | 74 | |
| | Week 28 retest | 73 | |
| | Week 28 retest | 74 | |
| | Week 28 retest | 83 | |
| | Week 40 | 78 | |
| | Week 52 | 76 | |
| | Week 64 | 90 | |
| | Week 76 | 85 | |
| | Week 88 | 76 | |
| | Week 100 | 74 | |
| 30-008 | Baseline | 231 | 69 year old male. The Investigator attributed the decreased platelet count at Week 88 to the patient hiking at high altitudes. |
| | Week 88 | 99 | |
| | Week 100 | 203 | |

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

### (6) Overall Safety Conclusions

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, and flushing continued to be the most commonly reported AE. Sixteen percent of patients discontinued prior to study completion, most due to an AE. Although the percentage of dropouts is lower for the extension study than for the 52-week study, it is noteworthy that a relatively high rate of discontinuations due to study medication intolerances (most commonly flushing and nausea) continued to be a problem during the second year of the study. This suggests that tolerance to the side-effects of Advicor, particularly flushing, does not substantially improve with long-term treatment as has previously been suggested. Mild elevations in AST, ALT, CPK, and FBS, and mild decreases in phosphorous were about as common in the extension study as in the 52-week study. Clinically significant laboratory abnormalities were uncommon, and 3 patients discontinued for a laboratory abnormality (two for glucose elevations, and one for a CPK elevation). Serious Adverse Events occurred in 25 patients (8%). The majority of these SAEs were cardiovascular events, which is not unexpected in this group of patients.

## E. Protocol MA-98-010409

*(Protocol MA-98-010409 will be referred to as MA-09 from this point forward)*

### 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 submitted to NDA #21-249 on 18-May-2001 as part of an 8-month safety update for Advicor. Protocol MA-09 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 106 patients who had previously completed either of the double-blind, controlled studies (MA-06 and MA-14). No efficacy findings were submitted, and the safety update contained safety data received by the sponsor prior to 01-Mar-2001 (database cut-off date).

#### 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 a Advicor dose of 500/20 once daily at bedtime for 4 weeks, and forced dose-titrated every 4 weeks as follows

**Table 133: 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

One hundred-six (106) patients were enrolled in the MA-09 study. 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. The MA-06 and MA-14 studies included treatment arms for Advicor, Niaspan alone, or lovastatin alone, so patients entering MA-09 were either previously exposed to Advicor or were Advicor naïve. Fifty-five (55) patients who were previously exposed to Advicor, and 51 patients who were Advicor-naïve were enrolled in the MA-09 study.

**a) Baseline Demographics**

Fifty-six (56%) of the patients who entered MA-09 were male, and 92% were Caucasian. Patients ranged in age from 28-78 years, with a mean age of 58.3. Demographic data are summarized in the following table

**Table 134: MA-09 Baseline Demographics**

| **Patients, n =** | 106 |
|---|---|
| **Demographic Measure** | |
| **Gender, n (%)** | |
| Male | 59 (56) |
| Female | 47 (44) |
| **Age, years** | |
| mean | 58.3 |
| median | 58.5 |
| min, max | 28, 78 |
| Age ≥ 65 years, n (%) | 35 (33) |
| **Ethnicity, n(%)** | |
| Caucasian | 98 (92) |
| Black | 6 (6) |
| Hispanic | 1 (1) |
| Asian | 1 (1) |
| **Mean BMI, kg/M$^2$** | 29.0 |

**b) Patient Disposition**

As of the database cut-off date (Mar-2001), the mean duration of treatment with study medication was 38 weeks, and 69 patients had received at least 48 weeks of study medication. Thirty-eight (38) patients (36%) had withdrawn from the study, and 30 of the 38 discontinuations were due to Adverse Events. When patients were divided by previous treatment in the MA-06 and MA-14 studies, patients who had previously received lovastatin or Niaspan were somewhat more likely to discontinue than patients who had previously received Advicor (42% and 40% of patients previously treated with lovastatin and Niaspan respectively vs 31% of patients previously treated with Advicor). Discontinuations for AEs were somewhat higher in the previously treated lovastatin (32%) group than in the previously treated Niaspan (25%) and Advicor (27%) groups. The reasons for patient discontinuations are summarized in the following table

**Table 135: MA-09 Patients Discontinued, Overall and by Previous Treatment**

| **Previous Treatment** | **All** | **Advicor** | **Lovastatin** | **Niaspan** |
|---|---|---|---|---|
| **Patients, n =** | 106 | 55 | 31 | 20 |
| **Number of Withdrawals, n (%)** | 38 (36) | 17 (31) | 13 (42) | 8 (40) |
| **Reason for Dropout, n (%)** | | | | |
| Adverse Event | 30 (28) | 15 (27) | 10 (32) | 5 (25) |
| Withdrew Consent | 2 (2) | 0 | 1 (3) | 1 (5) |
| Lost to Follow Up | 2 (2) | 1 (2) | 1 (3) | 0 |
| Other Medical | 4 (4) | 1 (2) | 1 (3) | 2 (10) |

The baseline demographics for the patients who dropped out were similar to the MA-09 study patients overall, except that dropouts were more likely than patients overall to have

been female (53% vs 44% respectively). Baseline demographics of patients overall vs dropouts is summarized in the following table

**Table 136: MA-09 Baseline Demographics of Patients Overall vs Dropouts**

| | Patients Overall | Dropouts |
|---|---|---|
| **Number of Patients, n =** | 106 | 38 |
| **Demographic Measure** | | |
| **Gender, n (%)** | | |
| Male | 59 (56) | 18 (47) |
| Female | 47 (44) | 20 (53) |
| **Age, years** | | |
| Mean | 58.3 | 59.5 |
| median | 58.5 | 61 |
| min, max | 28, 78 | 28, 78 |
| Age ≥ 65 years, n (%) | 35 (33) | 12 (32) |
| **Ethnicity, n (%)** | | |
| Caucasian | 98 (92) | 34 (89) |
| Black | 6 (6) | 3 (8) |
| Hispanic | 1 (1) | 0 |
| Asian | 1 (1) | 1 (3) |

## c) Safety Results

### (1) Adverse Events

A Treatment Emergent Adverse Event was defined by this Reviewer as any Adverse Event (AE) whose onset occurred after the initiation of study medication or increased in intensity or frequency after study medication was initiated, regardless of causality. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all randomized patients as the denominator. Clinical AEs were coded using the COSTART dictionary. Adverse Events were also analyzed by subgroups (male vs female, geriatric vs non-geriatric). There were too few non-Caucasians to evaluate by race. Common AEs were defined as having an incidence of ≥2% (A complete list of common AEs is contained in Appendix III).

There were 136 different AE terms reported by 92 of the 106 (87%) patients at any time during the study. The AE incidence rates by subgroup were similar to the incidence rate overall. Adverse Event incidence rates overall and by subgroup are as follows

**Table 137: MA-09 Incidence of Adverse Events, Overall and by Subgroup**

| | | Subgroup | | | |
|---|---|---|---|---|---|
| | **All** | **Male** | **Female** | **Geriatric** | **Non-Geriatric** |
| Number of Patients, n = | 106 | 59 | 47 | 35 | 71 |
| **Patients Reporting Any AE, n (%)** | 92 (87) | 52 (88) | 40 (85) | 30 (86) | 62 (87) |

### (2) Adverse Events by Body System

The most commonly reported AEs were in the Cardiovascular system, followed by Body as a Whole, the Digestive system, and Skin and Appendages. Flushing was the most commonly reported AE, reported by 40% of patients at any time during the study, and accounted for almost all of the Cardiovascular AEs. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table

**Table 138: MA-09 Incidence of Most Common Adverse Events by Body System**

| Patients, n = | | 106 |
|---|---|---|
| **Body System** | **COSTART Term** | n (%) |
| **Body as a Whole** | Infection | 18 (17) |
| | Flu syndrome | 10 (9) |
| | Injury, accidental | 10 (9) |
| | Pain | 10 (9) |
| | Pain, abdominal | 8 (8) |
| | Headache | 6 (6) |
| **Cardiovascular** | Flushing | 42 (40) |
| **Digestive** | Diarrhea | 11 (10) |
| | Dyspepsia | 9 (8) |
| | Nausea | 9 (8) |
| | GI disorder | 6 (6) |
| | Flatulence | 5 (5) |
| **Metabolic and Nutritional** | CPK, increased | 5 (5) |
| | Hyperglycemia | 5 (5) |
| **Respiratory** | Sinusitis | 6 ( 6) |
| | Rhinitis | 5 (5) |
| **Skin and Appendages** | Pruritis | 11 (10) |
| | Rash | 8 (8) |
| | Skin, dry | 6 (6) |

Adverse Events of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. Two patients (0410 and 2413) reported myalgias during the study. Patient 2413 was discontinued from the study due to myalgias. This patient had a peak CPK of 366 (>normal) at Week 24 which declined to 317 at the early termination visit. Patient 0410 was discontinued at Week 16 due to Herpes Zoster, and did not experience an elevation in CPK during the study. There were no reported cases of myopathy, rhabdomyolysis or hepatitis.

### (3) Adverse Events by Subgroup

Adverse Events were further analyzed by subgroups. Females were more likely than males to complain of flushing (53% vs 31% respectively). Geriatric patients were more likely than non-geriatric patients to complain of flushing (43% vs 32%) and infection (23% vs 14%). Non-geriatric patients were more likely than geriatric patients to complain of flu syndrome (13% vs 3%). As the number of patients in each subgroup is small, no definite conclusions will be drawn from this. The most common (>5% incidence) AEs overall and by subgroup are summarized as follows

**Table 139: MA-09 Incidence of Most Common Adverse Events Incidence, Overall and by Subgroup**

| | | All | Male | Female | Geriatric | Non-Geriatric |
|---|---|---|---|---|---|---|
| Patients, n = | | 106 | 59 | 47 | 35 | 71 |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | 18 (17) | 11 (19) | 7 (15) | 8 (23) | 10 (14) |
| | Flu syndrome | 10 (9) | 8 (14) | 2 (4) | 1 (3) | 9 (13) |
| | Injury, accidental | 10 (9) | 3 (5) | 7 (15) | 4 (11) | 6 (8) |
| | Pain | 10 (9) | 8 (14) | 2 (4) | 2 (6) | 8 (11) |
| | Pain, abdominal | 8 (8) | 4 (7) | 4 (9) | 4 (11) | 4 (6) |
| | Headache | 6 (6) | 3 (5) | 3 (6) | 1 (3) | 5 (7) |
| **Cardiovascular** | Flushing | 42 (40) | 18 (31) | 25 (53) | 15 (43) | 28 (32) |
| **Digestive** | Diarrhea | 11 (10) | 8 (14) | 3 (6) | 3 (8) | 8 (11) |
| | Dyspepsia | 9 (8) | 5 (8) | 4 (9) | 1 (3) | 8 (11) |
| | Nausea | 9 (8) | 3 (5) | 6 (13) | 4 (11) | 5 (7) |
| | GI disorder | 6 (6) | 3 (5) | 3 (6) | 2 (6) | 4 (6) |
| | Flatulence | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| **Metabolic and Nutritional** | CPK, increased | 5 (5) | 3 (5) | 2 (4) | 1 (3) | 4 (6) |
| | Hyperglycemia | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| **Respiratory** | Sinusitis | 6 ( 6) | 5 (8) | 1 (2) | 1 (3) | 5 (7) |
| | Rhinitis | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| **Skin and Appendages** | Pruritis | 11 (10) | 3 (5) | 8 (17) | 6 (17) | 5 (7) |
| | Rash | 8 (8) | 6 (10) | 2 (4) | 3 (8) | 5 (7) |
| | Skin, dry | 6 (6) | 5 (8) | 1 (2) | 1 (3) | 5 (7) |

### (4) Adverse Events Resulting in Drug Discontinuation

Thirty-eight (38) of 106 patients (36%) discontinued study medication prior to study completion. Of the 38 discontinuations, 30 were due to Adverse Events. The most commonly reported AE resulting in study drug discontinuation was flushing (10% of patients). Discontinuations due to AEs were also analyzed by subgroup. Female patients were more likely than male patients to discontinue for any reason (43% vs 31% respectively), and for an AE (34% vs 24%). Female patients were also more likely than males to discontinue for flushing (17% vs 5%). Geriatric and non-geriatric patients were about as likely to discontinue from the study for any reason and for an AE. Geriatric patients were more likely to discontinue for a CPK increase than non-geriatric patients (17% vs 1%). As the number of events per subgroup was small, no definite conclusions will be drawn from this. Patients were also divided by previous treatment received in the MA-06 and MA-14 studies. Discontinuations due to flushing were somewhat more likely in the group previously treated with lovastatin (5 patients, 16%) than in patients previously treated with Niaspan (2 patients, 10%) and Advicor (3 patients, 6%); however the number of patients per group was small. The most common (≥5%) reasons for discontinuation due to AEs overall and by subgroup are presented in the following table (A complete list of discontinuations due to AEs is listed in Appendix V).

**Table 140: MA-09 Discontinuations Due to Adverse Events, Most Common Overall and by Subgroup**

| | | | Subgroup | | | |
|---|---|---|---|---|---|---|
| | | All | Male | Female | Geriatric | Non-Geriatric |
| **Patients, n =** | | 106 | 59 | 47 | 35 | 71 |
| **All Discontinuations, n (%)** | | 38 (36) | 18 (31) | 20 (43) | 12 (34) | 26 (37) |
| **Discontinued for AE*, n (%)** | | 30 (28) | 14 (24) | 16 (34) | 11 (31) | 19 (27) |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Cardiovascular** | Flushing | 11 (10) | 3 (5) | 8(17) | 4 (11) | 7 (10) |
| **Digestive** | Diarrhea | 4 (4) | 2 (3) | 2 (4) | 4 (11) | 0 |
| | Dyspepsia | 4 (4) | 1 (2) | 3 (6) | 3 (9) | 1 (1) |
| **Metabolic and** | CPK increase | 7 (7) | 4 (7) | 3 (6) | 6 (17) | 1 (1) |
| **Nutritional** | Hyperuricemia | 4 (4) | 0 | 4 (9) | 2 (6) | 2 (3) |
| | Hyperglycemia | 3 (3) | 1 (2) | 2 (4) | 3 (9) | 0 |
| **Skin and** | Pruritis | 4 (4) | 1 (2) | 3 (6) | 3 (9) | 1 (1) |
| **Appendages** | Rash | 3 (3) | 0 | 3 (6) | 1 (3) | 2 (3) |
| **Discontinued for Lab abnormality** | | 6 (6) | 3 (5) | 3 (5) | 2 (6) | 4 (6) |

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

### (5) Serious Adverse Events

There were 7 Serious Adverse Events (SAEs) occurring in 6 patients. There were no deaths. Four (4) of the SAEs were in the Cardiovascular system, 2 in the Digestive system and one in the Musculoskeletal system. As there were a small number of SAEs, no conclusions will be drawn from this. The SAEs are listed in the following table

**Table 141: MA-09 Serious Adverse Events**

| Patient | M/F | Age (yrs) | Serious Adverse Event | Body System | Onset (days) | Investigator Attribution | Drug Discontinued? |
|---|---|---|---|---|---|---|---|
| 0301 | M | 71 | Acute appendicitis | Digestive | 308 | NR | N |
| 0801 | F | 75 | Chest pain/unstable angina | CV | 294 | NR | N |
| 1004 | M | 75 | Abnormal stress test/worsening CAD | CV | 280 | NR | N |
| 1008 | F | 67 | Biliary colic/cholelithiasis | Digestive | 91 | NR | N |
| 1310 | M | 75 | Possible brainstem infarction | CV | 175 | Possible | N |
| 1310 | M | 75 | Chest pain/worsening CAD | CV | 196 | NR | N |
| 1701 | M | 66 | Osteomyelitis | MS | 189 | NR | Y |

### (6) Treatment Emergent Adverse Events

Treatment emergent laboratory abnormalities (TELA) were defined by the sponsor as any laboratory abnormality "...commencing after initiation of study medication for which the baseline value was within normal limits." This Reviewer defined a TELA as any laboratory abnormality that worsened during study drug treatment regardless of the baseline value.

### (a) ALT and AST

Mild elevations from baseline in ALT and AST were common, and occurred in 15% and 36% of patients respectively at any time during the study. There were no elevations >3X

ULN during the study, and 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 142: MA-09 Incidence of Treatment Emergent ALT and AST Elevations**

| Patients, n = | 106 |
|---|---|
| ALT >normal, n (%) | 16 (15) |
| AST >normal, n (%) | 38 (36) |
| AST >2 X ULN, n (%) | 1 (1) |

**(b) Fasting Blood Sugar**

Mild elevations from baseline in FBS were common, and occurred in 50% of study patients at any time during the study. One patient (2413) was discontinued from the study due to FBS, CPK and uric acid elevations. No other patient was discontinued due to an elevated FBS, worsening HgA1C, or new diagnosis of diabetes. The incidence of treatment emergent FBS elevations are summarized in the following table

**Table 143: MA-09 Incidence of Treatment Emergent FBS Elevations**

| Patients, n = | 106 |
|---|---|
| FBS >normal, n (%) | 50 (47) |
| FBS >1.3 X ULN, n (%) | 11 (10) |
| FBS > 2 X ULN, n (%) | 1 (1) |

The patient discontinued (patient 2413) was a 62 year old female with a history of type 2 diabetes mellitus. Her FBS results are as follows

**Table 144: MA-09 Patient With Clinically Significant FBS Elevations**

| Week | FBS | Dose |
|---|---|---|
| Baseline | 148 | None |
| Week 4 | 132 | 500/20 X 4 weeks |
| Week 8 | 116 | 1000/40 X 7 weeks |
| Week 12 | 207 | 1500/40 X 4 weeks |
| Week 12 retest | 179 | 2000/40 X 5 weeks |
| Week 12 retest | 200 | Off study drug X 1 day |
| ET | 140 | Off study drug X 1 week |

**(c) Phosphorous**

Mild to moderate treatment emergent decreases in serum phosphorous were common, and occurred in 25% of patients. Serum phosphorous <normal was more common in males (32%) than females (17%). 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 overall and by subgroup (males vs females) are as follows

**Table 145: MA-09 Incidence of Treatment Emergent Phosphorous Decreases**

| | All | Male | Female |
|---|---|---|---|
| **Patients, n =** | 106 | 59 | 47 |
| **Phosphorous <normal, n (%)** | 27 (25) | 19 (32) | 8 (17) |
| **Phosphorous <2 X LLN, n (%)** | 5 ( 5) | 4 (7) | 1 (2) |

### (d) CPK

Mild elevations in CPK occurred in 35% of patients, and 1 patient had a CPK elevation >5 X ULN. Five (5) patients had study drug treatment discontinued due to CPK elevations. The incidence of CPK elevations is as follows

**Table 146: MA-09 Incidence of Treatment Emergent CPK Elevations**

| | |
|---|---|
| **Patients, n =** | 106 |
| **CPK >normal, n (%)** | 37 (35) |
| **CPK >5 X ULN, n (%)** | 1 (1) |

The five patients who were discontinued from the study due to CPK elevations are summarized in the following table

**Table 147: MA-07 Patients With Clinically Significant CPK Elevations**

| Week | CPK | Elevation | Dose | Contributing history |
|---|---|---|---|---|
| **Patient 1103** | | | | |
| Baseline | 321 | >normal | None | 54 year old male who complained of intermittent symptoms of gas, increased lethargy, increased hip pain, right ankle pain, numbness and shooting pain in the right arm, and increased back pain during the double-blind MA-14 study. Patient was discontinued from the MA-09 study after Week 12 for an elevated CPK. |
| Week 4 | 497 | >normal | 500/20 X 4 weeks | |
| Week 8 | 456 | >normal | 1000/40 X 4 weeks | |
| Week 12 | 596 | >normal | 1500/40 X 4 weeks | |
| Week 12 retest | 461 | >normal | 2000/40 X 4 weeks | |
| Week 12 retest | 249 | >normal | Off study drug X 1 week | |
| Week 12 retest | 582 | >normal | 1000/40 X 2 weeks | |
| ET | 499 | >normal | 1000/40 X 4 weeks | |
| ET retest | 409 | >normal | Off study drug X 2 weeks | |
| Et retest | 708 | >3 X ULN | Off study drug X 4 weeks | |
| ET retest | 307 | >normal | Off study drug X 7 weeks | |
| **Patient 1104** | | | | |
| Baseline | 434 | >normal | None | 45 year old male discontinued for an elevated CPK. There was no contributing history. |
| Week 4 | 439 | >normal | 500/20 X 4 weeks | |
| Week 8 | 561 | >normal | 1000/40 X 4 weeks | |
| Week 12 | 498 | >normal | 1500/40 X 4 weeks | |
| Week 24 | 865 | >3 X ULN | 2000/40 X 14 weeks | |
| Week 24 retest | 627 | >3 X ULN | Off study drug X 4 days | |
| Week 24 retest | 540 | >normal | Off study drug X 10 days | |
| Week 24 retest | 399 | >normal | Off study drug X 2 weeks | |
| Week 24 retest | 643 | >3 X ULN | 500/20 X 4 weeks | |
| ET | 545 | >normal | Off study drug X 1 week | |
| ET retest | 382 | >normal | Off study drug X 3 weeks | |
| **Patient 1806** | | | | |
| Baseline | 133 | | None | 71 year old female who experienced chronic lower back pain one week prior to Week 8. Eight weeks prior to Week 24, the patient experienced increased leg cramps that resolved prior to Week 36. The patient was discontinued from the study due to an elevated CPK. |
| Week 4 | 117 | | 500/20 X 4 weeks | |
| Week 8 | 238 | >normal | 1000/40 X 4 weeks | |
| Week 12 | 157 | | 1500/40 X 4 weeks | |
| Week 24 | 201 | >normal | 1500/40 X 9 weeks | |
| Week 36 | 274 | >normal | 1500/40 X 21 weeks | |
| ET | 208 | >normal | Off study drug X 1 week | |
| ET retest | 165 | >normal | Off study drug X 4 weeks | |
| **Patient 2405** | | | | 52 year old male who experienced an elevated CPK at Week 28 of the double-blind study (MA-06). The patient was enrolled in the MA-09 study before the CPK results for Week 28 were received. The patient was discontinued after 1 week of treatment in the MA-09 study due to the CPK elevation. |
| Baseline | 173 | | None | |
| Week 24 (MA-06) | 315 | >normal | 1000/20 X 15 weeks | |
| Week 24 retest | 146 | | 1000/20 X 17 weeks | |
| Week 28 (MA-06) | 912 | >3 X ULN | 1000/20 X 19 weeks | |
| ET | 128 | | Off study drug X 1 week | |
| **Patient 2413** | | | | |
| Baseline | 120 | | None | 62 year old female who experienced diffuse muscle aches at Week 8. The patient was discontinued from the study at about Week 24 for dyspepsia, diffuse muscle aches, and itchiness, and elevated FBS, CPK, and uric acid levels. |
| Week 4 | 187 | >normal | 500/20 X 4 weeks | |
| Week 8 | 163 | | 1000/40 X 7 weeks | |
| Week 12 | 308 | >normal | 1500/40 X 4 weeks | |
| Week retest | 196 | >normal | 1500/40 X 5 weeks | |
| Week retest | 256 | >normal | 2000/40 X 5 weeks | |
| Week 24 | 366 | >normal | Off study drug X 1 day | |
| ET | 317 | >normal | Off study drug X 1 week. | |

### (e) Other Laboratory Values

One additional patient (in addition to patient 2413 – see Table 147) was discontinued from the study due to an elevated uric acid level (Patient 1611; peak uric acid level 14.1). The patient was asymptomatic. No patient had an elevation >2 X ULN in alkaline phosphatase, LDH, or total bilirubin during study drug treatment, and no patient had a platelet count <100,000 during the study. Three (3) patients had amylase elevations >2 X ULN, all of whom were asymptomatic. All the amylase elevations resolved. Three (3) patients had elevated PT >2 X ULN. No contributing history was provided, and there were no reports of bleeding or other clinical sequelae in these patients. The 3 patients with PT elevations >2 X ULN are as follows

**Table 148: MA-09 Patients with PT >2 X ULN**

| Patient | Week | PT | PTT | PT Elevation |
|---|---|---|---|---|
| 2007 | Baseline | 13.00 | 24.50 | |
| | Week 24 | 93.00 | 24.60 | >3 X ULN |
| | Week 48 | 13.50 | 25.20 | >1.3 X ULN |
| 1406 | Baseline | 13.90 | 29.00 | >normal |
| | Week 24 | 11.10 | 25.00 | >normal |
| | Week 48 | 37.40 | 40.60 | >3 X ULN |
| 1805 | Baseline | 12.40 | 22.80 | |
| | Week 24 | 9.10 | 24.00 | |
| | ET | 25.60 | 67.80 | >2 X ULN |

### (7) Overall Safety Conclusions

The safety results for MA-09 were similar to those for the other clinical studies submitted to the NDA. Advicor was not well tolerated, and AEs were reported by 87% of study patients at anytime during the study. Cardiovascular system AEs were the most commonly reported, almost all of which were complaints of flushing. Thirty-eight (38) of the 106 patients (36%) discontinued prior to study completion, with 30 patients (28%) 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 TELAs were uncommon. Six (6) patients (6%) discontinued due to laboratory abnormalities, which were due to elevations in FBS, CPK and uric acid.

The dropout rate for MA-09 was similar to the dropout rates for MA-14, MA-06 and MA-07. This is particularly noteworthy as patients in MA-09 were enrolled only after successful completion of MA-14 and MA-06. As more than half of the MA-09 patients had previously been exposed to Advicor, then the high-rate of discontinuations, mainly due to AEs, suggests that intolerance to Advicor's side-effects continues to a problem for a large proportion of patients despite prolonged exposure to the drug.

## IV. Conclusions on Review of NDA 21-249

### A. Efficacy Conclusions

The findings of the two controlled clinical studies, MA-14 and MA-06, do not support Advicor as a first-line drug treatment for LDL-lowering. The review of MA-14 raised several problems with the study that made the efficacy results uninterpretable and non-supportive of the proposed label. The MA-06 review showed that treatment with Advicor produced LDL-lowering that was significantly better than lovastatin alone only after 24 weeks of titration to a dose of 2000/40. Additionally, on subgroup analysis, it was observed that the LDL-lowering efficacy of Advicor over lovastatin was only applicable to female patients. Male patients had no better results for LDL-lowering with Advicor than they did with lovastatin alone.

The MA-06 efficacy results however, do support Advicor as a convenient product for patients who require treatment of elevated cholesterol and triglyceride levels and low HDL-C levels that are not effectively treated with single agent therapy. Advicor was significantly better at LDL-lowering than Niaspan alone, and was significantly better at TG-lowering and HDL-raising than either Niaspan or lovastatin monotherapy. Although the MA-06 study results were not reproduced in a second controlled trial, there is sufficient clinical experience with the marketed products Niaspan and Mevacor to support a combination tablet of these two products.

The long-term, uncontrolled study MA-07 also found that Advicor produced dose-dependent decreases in LDL-C and TG, and increases in HDL-C. These results were durable over the 52 weeks of the study.

### B. Safety Conclusions

The safety findings in both the controlled and uncontrolled clinical studies suggest that Advicor is relatively safe for chronic administration. The majority of Adverse Events were not serious, and resolved when Advicor was discontinued or the dose was decreased. Advicor was poorly tolerated however, resulting in a high-drop out rate that continued into year 2 of the MA-07 extension study. This is a limitation for any drug intended for treatment of a chronic condition. Advicor's side-effect profile was similar to that of Niaspan and other niacin products. However, as Advicor is a combination product, it is recommended that the Advicor label contain the same precautions, warnings, and contraindications as are contained in both the Mevacor and Niaspan labels.

## V. Reviewer's Comments on Proposed Labeling

The Sponsor is proposing Advicor as first-line lipid-lowering therapy for hypercholesterolemia and dyslipidemia (type IIa and IIb). The Sponsor has also proposed numerous indications for Advicor in the label, including _____ _____ that are not supported by the data submitted to the NDA. This Reviewer is in disagreement with large portions of the Sponsor's proposed label, and recommended changes to the label are discussed below. As discussions with the Sponsor regarding the proposed labeling are ongoing at the time of this writing, comments on the proposed labeling may not be final.

### A. Clinical Pharmacology

_____ claims cannot be made for Advicor. Deletion of the following sentence is recommended:

- [ ]

Clinical endpoint studies have also not been performed for _____ _____. Deletion of the following sentence is recommended:

- [ ]

It is recommended that the following sentence be added:

- The effect of combined therapy with niacin and lovastatin on cardiovascular morbidity and mortality has not been determined.

### B. Mechanism of Action

It is recommended by Pharm-Tox (see Pharm-Tox review) that the following sentences be removed

- [ ]

### C. Pharmacokinetics

It is recommended by Biopharm (see Biopharm review) that the following paragraph be re-written as follows:
Under Absorption and Bioavailability

- [ ]

[ ]

Under Elimination

- Niacin is primarily excreted in urine mainly as metabolites.

Further revisions in the Pharmacokinetic labeling would be at the discretion of the Biopharm Reviewer.

**D. Clinical Studies**

The MA-06 study is the only double-blind controlled study that supports the proposed tablet strengths and dosing for Advicor. The clinical studies section should therefore reflect the efficacy findings in MA-06 alone. This section should include the LDL-C, HDL-C and TG mean percent change from baseline for Advicor, Niaspan and lovastatin from the Division's statistical review in tabular form (see table 8 in the Statistical Review and Evaluation). In addition, comparison of Advicor to its individual components Niaspan and lovastatin showed that

- Only after 28 weeks of titration to Advicor 2000/40 was LDL-lowering greater than that achieved with lovastatin monotherapy (p-value .04)
- Advicor at doses ——— or higher achieved greater LDL-lowering than Niaspan (p-value .0001), and
- The treatment effects of Advicor compared to lovastatin and Niaspan differed for males and females with a significantly larger treatment effect seen for females. It is recommended that a table summarizing the mean percent change from baseline at endpoint for LDL-C, HDL-C and TG by gender be included.

Efficacy findings from the ———————————————
should be removed from the label, as ——— does not support the proposed labeling.

The long-term study MA-07 was an open-label uncontrolled study. Efficacy data from MA-07 support the finding that the lipid-altering effects of Advicor were similar to those of MA-06 and were maintained throughout 52 weeks of treatment. As, the mean percent changes in LDL-C, HDL-C and TG have already been summarized from the controlled trial MA-06, the ———————— from MA-07 is redundant and it is recommended that it be removed.

The sponsor has also proposed including ———————————————
———————————————

There are no objective data to support clinical endpoint claims for combination therapy with niacin and lovastatin, and it is unknown if the findings for monotherapy with either agent alone also apply to combination therapy. It is therefore recommended that ———
——— be removed from the label.

The sponsor is also proposing including the [redacted]. Once again, there are no available clinical data to support these claims for Advicor, and it is recommended that [redacted] be removed from the label.

[redacted] Therefore, the [redacted] should also not appear in the Advicor label.

**E. Indications and Usage**

Advicor is a fixed dose combination product and is not indicated for initial therapy [redacted]

[redacted] Advicor [redacted] indication for the treatment of primary hypercholesterolemia and mixed dyslipidemia in

- Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen, and
- Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen.
- [redacted]

[redacted]

It is recommended that the Indications and Usage section be re-written to reflect these changes.

**F. General Recommendation**

It is recommended that the NCEP guidelines be removed from the label. The NCEP III guidelines were recently updated, and it is expected that guidelines will change periodically, possibly rendering the labeling recommendations obsolete.

**G. Contraindications**

It is recommended by Pharmtox that the Pregnancy and Lactation section include the following:

- [ Advicor may cause fetal harm when administered to pregnant women. ]

**H. Warnings**

Under Liver Dysfunction section, it is recommended that the incidence of transaminase elevations for Niaspan alone and lovastatin alone also be included.

Under Myopathy Caused by Drug Interactions section, it is recommended that niacin be included in the list of drugs that may increase the incidence and severity of myopathy with concomitant administration with lovastatin. It is also recommended that large quantities of grapefruit be included as a CYP 3A4 inhibitor.

Under Reducing the Risk of Myopathy section, the following addition is suggested:

- Physicians contemplating the use of Advicor ——— should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial month of treatment or during any period of upward dosage titration of either drug.
- The ——— use of Advicor ——— with fibrates should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination.

These suggested changes are consistent with the current warnings in the Niaspan and Mevacor labels. There were no new clinical data submitted to this NDA to warrant the removal of precautions for combination lipid-altering therapy.

**I. Precautions**

It has been shown that niacin use is associated with FBS elevations, glucose intolerance, and worsening glucose control in diabetes. Glucose abnormalities were observed frequently in the Advicor controlled and uncontrolled studies. It is recommended that the Precautions section include the incidence rates of glucose abnormalities, and a warning that [ ]

Platelet count and serum phosphorous decreases have also been associated with niacin. Some patients experienced platelet counts <100,000 in the Advicor studies, and phosphorous decreases were common, particularly in male patients. It is recommended that the label include these findings.

Under the Pregnancy section, Pharmtox has recommended the following addition:

[ ]

Under Geriatric Use section, it is recommended that the Geriatric findings reflect the findings in the double-blind controlled study MA-06, and not ———

[redacted]. This Reviewer did not find any significant differences in types and frequencies of AEs in geriatric and non-geriatric patients.

**J. Adverse Reactions**

This Reviewer did not find Advicor to be well-tolerated, and approximately 1/3 of patients discontinued study participation in all studies submitted, mostly due to AEs. The most common AEs were assessed objectively in the double-blind controlled studies. It is therefore recommended that a tabular presentation of the most common AEs, with comparisons to the active comparators niacin and lovastatin, be presented with data from either MA-06, MA-14 or both, and not include the [redacted]. It is also recommended that AEs be presented without filtering for causality as this is a more objective presentation of the data.

In addition, no comparisons of Advicor to [redacted] were made in the Advicor clinical program, and it is suggested that the comparison of flushing frequency and severity for Advicor to [redacted] be deleted.

**K. Dosage and Administration**

As it is recommended that Advicor be approved as a second-line convenient product rather than as first-line drug therapy, the following changes are suggested:

- For patients not already receiving Niaspan, the usual starting dose is 500 mg qhs, and is titrated up by 500 mg every 4 weeks, to a maximum dose of 2000 mg a day.
- For patients not already receiving lovastatin, the usual starting dose is 20 mg, with dose adjustments made at intervals of 4 weeks or more.
- Patients receiving lovastatin who may benefit from the addition of niacin therapy should receive dosage titration with Niaspan, and then may receive an equivalent (based on the Niaspan component) of Advicor once a stable niacin dose has been reached.
- [redacted]

## VI. Review of Financial Disclosure

Financial disclosure information was reviewed for the two controlled clinical studies MA-14 and MA-06. There were no financial disclosures submitted for any of the uncontrolled studies.

### A. Protocol MA-98-010406

There were 23 Principal Investigators at 23 sites nationally. All 23 Investigators (100%) submitted financial disclosure information. None of the Investigators were employees of Kos Pharmaceuticals, and no Investigator had a significant equity interest in Kos Pharmaceuticals.

[

]

Comments: Protocol MA-06 was a double-blind, placebo-controlled study. The blind was maintained throughout the study. Lipid results were also blinded to the study Investigators. The financial bias at these study centers is unlikely to have affected the results of the study.

### B. Protocol MA-98-010414

There were 14 Principal Investigators and 4 Co-Investigators at 16 sites nationally. All 18 Investigators (100%) submitted financial disclosure information. None of the Investigators were employees of Kos Pharmaceuticals, and no Investigator received any

Comments: Protocol MA-14 was a double-blind, placebo-controlled study. The blind was maintained throughout the study. Lipid results were also blinded to the study Investigators. The financial bias at this study center is unlikely to have affected the results of the study.

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## VII. Recommendations

The data from the clinical safety and efficacy studies submitted to NDA 21-249 do not support the Sponsor's proposed indication of Advicor as a first-line drug treatment for LDL-lowering, and it is recommended that Advicor not receive approval for this indication. Review of the clinical efficacy data show:

1. No additional benefit to LDL-lowering was seen for Advicor over lovastatin alone to support the proposed dosage strengths 500/20, 750/20, ———————
2. No additional benefit to LDL-lowering was seen for Advicor over lovastatin alone for male patients at any dose.

It is recommended that Advicor receive approval as a combination product for patients who may require treatment of elevated cholesterol and triglyceride levels and decreased HDL-C levels.

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APPEARS THIS WAY
ON ORIGINAL

# VIII. Appendices

## A. Appendix I: Concomitant Medication Use

### 1. Study MA-14

**Table 149: MA-14 Most Commonly Reported Concomitant Medications**

| | | Treatment | | | | |
|---|---|---|---|---|---|---|
| | **All** | **Niaspan** | **Advi/10** | **Advi/20** | **Advi/40** | **Lovastatin** |
| Randomized Patients, n = | 164 | 31 | 34 | 34 | 32 | 33 |
| **Concomitant Medication** | | | | | | |
| Aspirin, n (%) | 88 (54) | 16 (52) | 21 (62) | 21 (62) | 16 (50) | 15 (46) |
| Multivitamin, n (%) | 42 (26) | 10 (32) | 7 (21) | 8 (24) | 7 (22) | 10 (30) |
| Vitamin E, n (%) | 36 (22) | 8 (26) | 4 (12) | 11 (32) | 4 (13) | 9 (27) |
| Calcium, n (%) | 27 (16) | 8 (26) | 4 (12) | 3 (9) | 4 (13) | 8 (24) |
| Vitamin C | 26 (16) | 7 (23) | 4 (12) | 6 (18) | 4 (13) | 5 (15) |
| Ibuprofen, n (%) | 22 (13) | 3 (10) | 3 (9) | 5 (15) | 6 (19) | 5 (15) |
| Atenolol, n (%) | 21 (13) | 4 (13) | 5 (15) | 3 (9) | 4 (13) | 5 (15) |
| Acetaminophen, n (%) | 20 (12) | 4 (13) | 3 (9) | 5 (15) | 2 (6) | 6 (18) |
| Nitroglycerine, n (%) | 16 (10) | 3 (10) | 3 (9) | 4 (12) | 4 (13) | 2 (6) |
| Estrogen, n (%) | 16 (10) | 3 (10) | 7 (21) | 1 (3) | 3 (9) | 2 (6) |
| Amlodipine, n (%) | 15 (9) | 4 (13) | 4 (12) | 3 (9) | 2 (6) | 2 (6) |
| Lisinopril, n (%) | 14 (9) | 2 (6) | 3 (9) | 2 (6) | 6 (19) | 1 (3) |
| Levothyroxine, n (%) | 11 (7) | 1 (3) | 3 (9) | 1 (3) | 2 (6) | 4 (12) |
| Hydrochlorothiazide, n (%) | 11 (7) | 2 (6) | 5 (15) | 3 (9) | 1 (3) | 0 |
| Metoprolol, n (%) | 10 (6) | 0 | 2 (6) | 3 (3) | 3 (9) | 2 (6) |
| Furosemide, n (%) | 9 (5) | 3 (10) | 2 (6) | 1 (3) | 2 (6) | 1 (3) |
| Pseudoephedrine, n (%) | 9 (5) | 3 (10) | 1 (3) | 3 (9) | 1 (3) | 1 (3) |
| TMP/SMX n (%) | 8 (5) | 2 (6) | 1 (3) | 3 (9) | 1 (3) | 1 (3) |

## 2. Study MA-06

**Table 150: MA-06 Most Commonly Reported Concomitant Medications**

| | | Treatment | | | |
|---|---|---|---|---|---|
| | **All** | **Advi/20** | **Advi/40** | **Niaspan** | **lovastatin** |
| ITT Patients, n = | 236 | 57 | 57 | 61 | 61 |
| **Concomitant medication, n (%)** | | | | | |
| Aspirin | 144 (61) | 37 (65) | 32 (56) | 37 (61) | 38 (62) |
| Multivitamin | 84 (36) | 18 (32) | 24 (42) | 23 (38) | 19 (31) |
| Vitamin E | 74 (31) | 14 (25) | 19 (33) | 21 (34) | 20 (33) |
| Vitamin C | 56 (24) | 16 (28) | 13 (23) | 15 (25) | 12 (20) |
| Calcium | 32 (14) | 5 (9) | 12 (21) | 7 (11) | 8 (13) |
| Estrogen | 30 (13) | 5 (9) | 9 (16) | 7 (11) | 9 (15) |
| Atenolol | 29 (12) | 4 (7) | 8 (14) | 12 (20) | 5 (8) |
| Ibuprofen | 27 (11) | 8 (14) | 8 (14) | 5 (8) | 6 (10) |
| Nitroglycerin | 23 (10) | 5 (9) | 4 (7) | 7 (11) | 7 (11) |
| Hydrochlorothiazide | 20 (8) | 6 (11) | 3 (5) | 4 (7) | 7 (11) |
| Acetaminophen | 18 (8) | 5 (9) | 4 (7) | 5 (8) | 4 (7) |
| Folic acid | 17 (7) | 4 (7) | 4 (7) | 3 (5) | 6 (10) |
| Levothyroxine | 17 (7) | 6 (11) | 5 (9) | 3 (5) | 3 (5) |
| Metformin | 15 (6) | 5 (9) | 3 (5) | 3 (5) | 4 (7) |
| Amlodipine | 15 (6) | 3 (5) | 3 (5) | 5 (8) | 4 (7) |
| Lisinopril | 13 (6) | 2 (4) | 4 (7) | 3 (5) | 4 (7) |
| Diltiazem | 13 (6) | 3 (5) | 5 (9) | 1 (2) | 4 (7) |
| Influenza vaccine | 12 (5) | 2 (4) | 4 (7) | 1 (2) | 5 (8) |
| Metoprolol | 12 (5) | 4 (7) | 1 (2) | 2 (3) | 5 (8) |
| Amoxicillin | 11 (5) | 1 (2) | 3 (5) | 2 (3) | 5 (8) |
| Furosemide | 11 (5) | 1 (2) | 5 (9) | 1 (2) | 4 (7) |

## 3. Study MA-07

**Table 151: MA-07 Most Commonly Reported Concomitant Medications**

| ITT Patients, n = | 814 |
|---|---|
| **Concomitant Medication** | n (%) |
| Aspirin | 632 (78) |
| Multivitamin | 254 (31) |
| Vitamin E | 202 (25) |
| Ibuprofen | 157 (19) |
| Vitamin C | 139 (17) |
| Acetaminophen | 130 (16) |
| Nitroglycerin | 129 (16) |
| Calcium | 125 (15) |
| Estrogen | 87 (11) |
| Atenolol | 82 (10) |
| Metoprolol | 77 (9) |
| Lisinopril | 67 (8) |
| Potassium | 56 (7) |
| Levothyroxine | 56 (7) |
| Naproxen | 52 (6) |
| Diphenhydramine | 50 (6) |
| Amoxicillin | 50 (6) |
| Amlodipine | 49 (6) |
| Flu vaccine | 49 (6) |
| Omeprazole | 49 (6) |
| Ranitidine | 48 (6) |
| Albuterol | 46 (6) |
| Lansoprazole | 46 (6) |
| Loratadine | 46 (6) |
| Diltiazem | 44 (5) |
| Hydrochlorothiazide | 43 (5) |
| Hydrocodone | 40 (5) |
| Metformin | 38 (5) |
| Furosemide | 38 (5) |
| Cephalexin | 37 (5) |

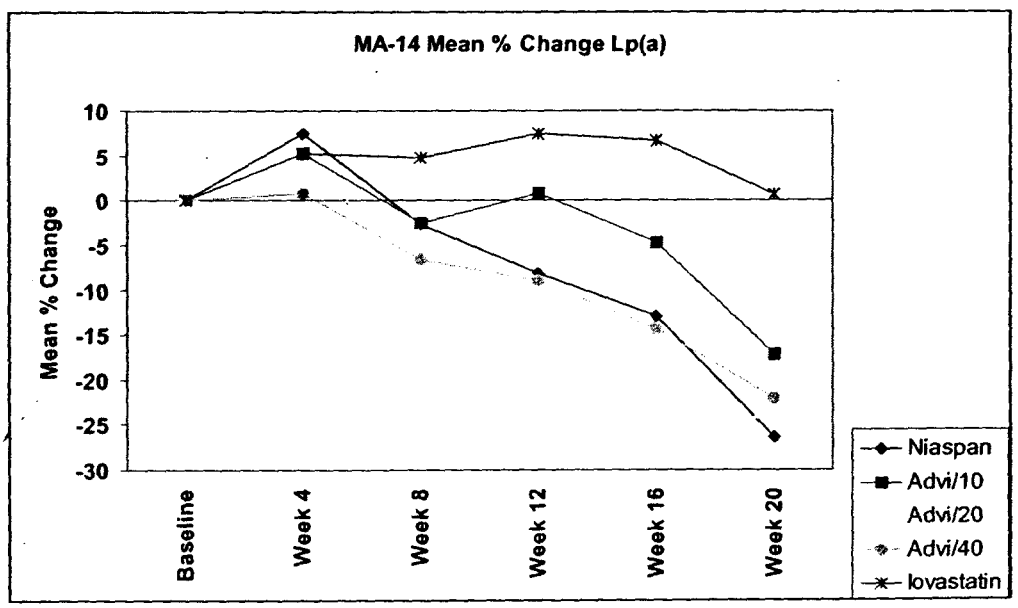
## B. Appendix II: Lp(a) Results

### 1. Study MA-14

**Table 152: MA-14 Mean % Change Lp(a)**

| Treatment | Baseline | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 |
|---|---|---|---|---|---|---|
| **Niaspan: dose (mg)** | | **500** | **1000** | **1500** | **2000** | **2500** |
| n | 31 | 28 | 27 | 26 | 25 | 23 |
| Mean | 39.4 mg/dL | +7.4% | -2.7% | -8.2% | -13.0% | -26.3% |
| SE | 7.86 | 5.05 | 5.08 | 5.55 | 10.91 | 5.64 |
| **Advi10: dose (mg/mg)** | | **500/10** | **1000/10** | **1500/10** | **2000/10** | **2500/10** |
| n | 34 | 32 | 32 | 31 | 30 | 30 |
| Mean | 45.6 mg/dL | +5.3% | -2.5% | +0.9% | -4.7% | -17.2% |
| SE | 8.61 | 6.03 | 5.38 | 6.71 | 10.17 | 6.96 |
| **Advi/20: dose (mg/mg)** | | **500/20** | **1000/20** | **1500/20** | **2000/20** | **2500/20** |
| n | 34 | 33 | 30 | 26 | 26 | 24 |
| Mean | 50.0 mg/dL | +2.9% | -4.6% | -13.8% | -20.9% | -25.0% |
| SE | 8.64 | 4.25 | 4.21 | 5.36 | 5.17 | 5.91 |
| **Advi/40: dose (mg/mg)** | | **500/40** | **1000/40** | **1500/40** | **2000/40** | **2500/40** |
| n | 32 | 29 | 27 | 23 | 23 | 23 |
| Mean | 36.4 mg/dL | +0.8% | -6.6% | -9.0% | -14.3% | -22.1% |
| SE | 6.14 | 4.53 | 3.74 | 6.88 | 5.90 | 4.75 |
| **Lovastatin: dose (mg)** | | **10** | **10** | **20** | **20** | **40** |
| n | 33 | 31 | 29 | 29 | 29 | 29 |
| Mean | 46.0 mg/dL | +5.2% | +4.8% | +7.5% | +6.7% | +0.7% |
| SE | 5.82 | 2.46 | 3.69 | 4.56 | 4.25 | 3.58 |

**Figure 13: MA-14 Mean % Change Lp(a)**

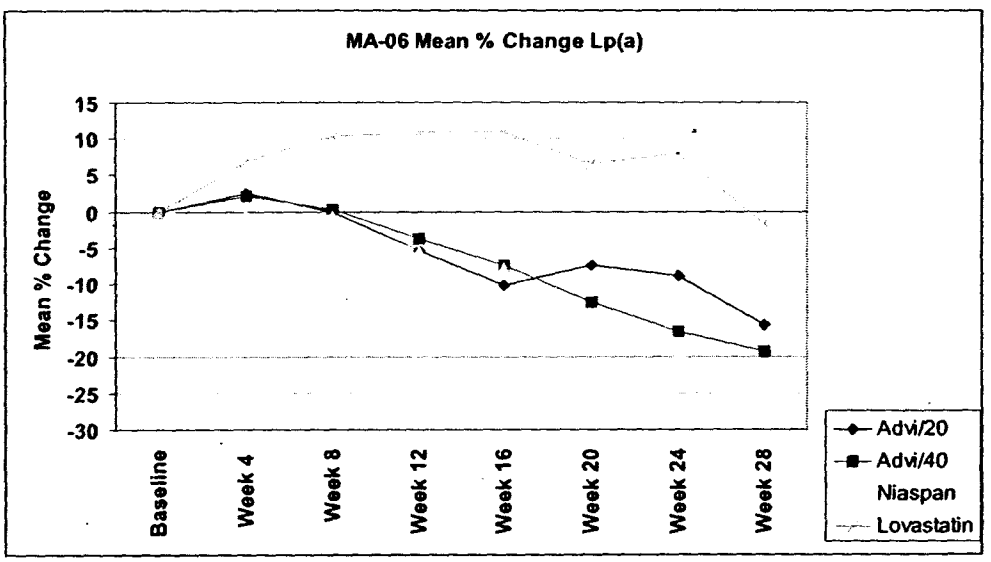


## 2. Study MA-06

**Table 153: MA-06 Mean % Change Lp(a)**

| | | Week | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Treatment** | **Baseline** | **4** | **8** | **12** | **16** | **20** | **24** | **28** |
| Advi/20: Dose (mg/mg) | | 500/20 | 750/20 | 1000/20 | 1000/20 | 1000/20 | 1000/20 | 1000/20 |
| n | 57 | 54 | 49 | 48 | 43 | 42 | 42 | 40 |
| Mean | 32.4 mg/dL | +2.6% | -0.1% | -5.3% | -10.2% | -7.4% | -8.8% | -15.7% |
| SE | 5.16 | -1.1 | 4.09 | 4.21 | 4.36 | 3.86 | 3.91 | 3.91 |
| Advi/40: Dose (mg/mg) | | 500/20 | 750/20 | 1000/20 | 1000/40 | 1500/40 | 2000/40 | 2000/40 |
| n | 57 | 52 | 48 | 47 | 45 | 42 | 42 | 42 |
| Mean | 34.3 mg/dL | +2.2% | +0.3% | -3.7% | -7.4% | -12.6% | -16.6% | -19.3% |
| SE | 4.76 | 3.66 | 4.48 | 3.96 | 3.77 | 5.05 | 4.25 | 3.85 |
| Niaspan: Dose (mg) | | 500 | 750 | 1000 | 1000 | 1500 | 2000 | 2000 |
| n | 61 | 56 | 51 | 46 | 44 | 43 | 42 | 41 |
| Mean | 41.0 mg/dL | -0.4% | -0.6% | -5.4% | -7.8% | -14.9% | -19.7% | -24.5% |
| SE | 5.11 | 2.61 | 3.56 | 4.47 | 3.85 | 4.50 | 3.87 | 3.84 |
| Lovastatin: Dose (mg) | | 20 | 20 | 20 | 40 | 40 | 40 | 40 |
| n | 61 | 59 | 58 | 56 | 56 | 54 | 53 | 53 |
| Mean | 42.3 mg/dL | +6.9% | +10.4% | +11.0% | +11.0% | +6.6% | +8.0% | -1.8% |
| SE | 5.35 | 3.12 | 3.47 | 3.85 | 3.68 | 4.05 | 3.68 | 4.18 |

**Figure 14: MA-06 Mean % Change Lp(a)**




## 3. Study MA-07

**Table 154: MA-07 Mean % Change Lp(a)**

| | | | 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** |
| **Observed Cases, n =** | | 93 | 92 | 95 | 87 | 0 | 0 | 0 | 0 |
| **Lp(a)** | Mean | 42.8 | +5.5 | +1.7 | -10.5 | - | - | - | - |
| | SE | 4.35 | 10.53 | 11.01 | 8.42 | | | | |

## C. Appendix III: Common Adverse Events by Body System

### 1. Study MA-14

**Table 155: MA-14 Incidence of Common (≥2%) AEs by Body System**

| | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | All | Niaspan | Advi/10 | Advi/20 | Advi/40 | Lovastatin |
| Randomized Patients, n = | | 164 | 31 | 34 | 34 | 32 | 33 |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | 24 (14.6) | 4 (12.1) | 4 (11.8) | 4 (11.8) | 5 (15.6) | 7 (21.2) |
| | Asthenia | 12 (7.3) | 3 (9.7) | 3 (8.8) | 1 (2.9) | 2 (6.3) | 3 (9.1) |
| | Pain | 12 (7.3) | 3 (9.7) | 3 (8.8) | 2 (5.9) | 1 (3.1) | 3 (9.1) |
| | Headache | 9 (5.5) | 3 (9.7) | 1 (2.9) | 2 (5.9) | 1 (3.1) | 2 (6.1) |
| | Flu syndrome | 8 (4.9) | 4 (12.1) | 1 (2.9) | 3 (8.8) | 0 | 0 |
| | Pain, abdominal | 8 (4.9) | 1 (3.2) | 0 | 3 (8.8) | 2 (6.3) | 2 (6.1) |
| | Pain, back | 5 (3.0) | 1 (3.2) | 0 | 2 (5.9) | 2 (6.3) | 0 |
| | Injury, accidental | 4 (2.4) | 1 (3.2) | 1 (2.9) | 0 | 1 (3.1) | 1 (3.0) |
| | Pain, chest | 4 (2.4) | 0 | 1 (2.9) | 0 | 1 (3.1) | 2 (6.1) |
| **Cardiovascular** | Flushing | 86 (52.4) | 20 (64.5) | 18 (52.9) | 22 (64.7) | 21 (65.6) | 5 (15.2) |
| | Hypertension | 5 (3.0) | 1 (3.2) | 2 (5.9) | 0 | 1 (3.1) | 1 (3.0) |
| | Syncope | 5 (3.0) | 1 (3.2) | 1 (2.9) | 1 (2.9) | 1 (3.1) | 1 (3.0) |
| | Palpitations | 4 (2.4) | 1 (3.2) | 1 (2.9) | 0 | 1 (3.1) | 1 (3.0) |
| **Digestive** | Nausea | 14 (8.5) | 7 (22.6) | 1 (2.9) | 2 (5.9) | 2 (6.3) | 2 (6.1) |
| | Diarrhea | 12 (7.3) | 6 (19.4) | 0 | 4 (11.8) | 2 (6.3) | 0 |
| | Vomiting | 8 (4.9) | 4 (12.1) | 0 | 2 (5.9) | 2 (6.3) | 0 |
| | Dyspepsia | 7 (4.3) | 3 (9.7) | 0 | 1 (2.9) | 1 (3.1) | 2 (6.1) |
| **Metabolic and Nutritional** | Hyperglycemia | 5 (3.0) | 2 (6.5) | 2 (5.9) | 1 (2.9) | 0 | 0 |
| | SGOT increase | 4 (2.4) | 0 | 1 (2.9) | 1 (2.9) | 2 (6.3) | 0 |
| **Musculoskeletal** | Cramps, legs | 5 (3.0) | 2 (6.5) | 1 (2.9) | 0 | 0 | 2 (6.1) |
| **Nervous** | Insomnia | 5 (3.0) | 0 | 3 (8.8) | 0 | 0 | 2 (6.1) |
| | Dizziness | 4 (2.4) | 0 | 2 (5.9) | 0 | 0 | 2 (6.1) |
| **Respiratory** | Sinusitis | 6 (3.7) | 1 (3.2) | 1 (2.9) | 1 (2.9) | 2 (6.3) | 1 (3.0) |
| **Skin and Appendages** | Pruritis | 12 (7.3) | 4 (12.1) | 1 (2.9) | 3 (8.8) | 2 (6.3) | 2 (6.1) |
| | Rash | 9 (5.5) | 2 | 1 (2.9) | 3 (8.8) | 2 (6.3) | 1 (3.0) |
| **Urogenital** | Infection, urinary tract | 5 (3.0) | 1 (3.2) | 1 (2.9) | 3 (8.8) | 0 | 0 |

## 2. Study MA-06

**Table 156 : MA-06 Incidence of Common (≥2%) AEs by Body System**

| | | | Treatment | | | |
|---|---|---|---|---|---|---|
| | | All | Advi/20 | Advi/40 | Niaspan | lovastatin |
| ITT Patients, n = | | 236 | 57 | 57 | 61 | 61 |
| **Body System** | **COSTART Term** | | | | | |
| **Body as a Whole** | Infection | 52 (22) | 17 (30) | 13 (23) | 10 (16) | 12 (20) |
| | Headache | 28 (12) | 11 (19) | 5 (9) | 9 (15) | 3 (5) |
| | Pain | 23 (10) | 4 (7) | 8 (4) | 5 (8) | 6 (10) |
| | Flu Syndrome | 15 (6) | 3 (5) | 5 (9) | 3 (5) | 4 (7) |
| | Pain, Back | 15 (6) | 6 (11) | 0 | 4 (7) | 5 (8) |
| | Injury, Accidental | 10 (4) | 2 (4) | 2 (4) | 3 (5) | 3 (5) |
| | Asthenia | 9 (4) | 2 (4) | 2 (4) | 3 (5) | 2 (3) |
| | Pain, Abdomen | 8 (3) | 3 (5) | 1 (2) | 0 | 4 (7) |
| | Pain, Chest | 4 (2) | 0 | 2 (4) | 1 (2) | 1 (2) |
| **Cardiovascular** | Flushing | 148 (63) | 47 (82) | 47 (82) | 42 (69) | 12 (20) |
| **Digestive System** | Nausea | 13 (6) | 3 (5) | 6 (11) | 4 (7) | 0 |
| | Diarrhea | 11 (5) | 3 (5) | 4 (7) | 2 (3) | 2 (3) |
| | Dyspepsia | 9 (4) | 2 (4) | 2 (4) | 3 (5) | 2 (3) |
| | Constipation | 5 (2) | 2 (4) | 0 | 2 (3) | 1 (2) |
| | GI Distress | 5 (2) | 1 (2) | 0 | 3 (5) | 1 (2) |
| | Flatulance | 4 (2) | 3 (5) | 0 | 0 | 1 (2) |
| | Vomiting | 4 (2) | 2 (4) | 1 (2) | 1 (2) | 0 |
| **Hematologic and Lymphatic** | Ecchymosis | 4 (2) | 2 (4) | 1 (2) | 0 | 1 (2) |
| **Metabolic and Endocrine** | Hyperglycemia | 15 (6) | 3 (5) | 2 (4) | 4 (7) | 6 (10) |
| | Edema, peripheral | 10 (4) | 2 (4) | 4 (7) | 1 (2) | 3 (5) |
| | CPK Increase | 5 (2) | 3 (5) | 1 (2) | 0 | 1 (2) |
| **Musculoskeletal** | Myalgia | 16 (7) | 3 (5) | 2 (4) | 4 (7) | 7 (11) |
| | Arthritis | 7 (3) | 1 (2) | 3 (5) | 0 | 3 (5) |
| | Cramps, Leg | 6 (3) | 1 (2) | 1 (2) | 2 (3 | 2 (3) |
| **Nervous System** | Insomnia | 11 (5) | 4 (7) | 2 (4) | 3 (5) | 2 (3) |
| | Dizziness | 10 (4) | 3 (5) | 2 (4) | 3 (5) | 2 (3) |
| | Paresthesias | 6 (3) | 1 (2) | 2 (4) | 2 (3) | 1 (2) |
| | Hypertonia | 4 (2) | 0 | 1 (2) | 1 (2) | 2 (3) |
| **Respiratory** | Cough, Increased | 9 (4) | 1 (2) | 4 (7) | 3 (5) | 1 (2) |
| | Pharyngitis | 7 (3) | 0 | 2 (4) | 3 (5) | 2 (3) |
| | Rhinitis | 7 (3) | 0 | 2 (4) | 3 (5) | 2 (3) |
| | Sinusitis | 6 (3) | 3 (5) | 2 (4) | 0 | 1 (2) |
| **Skin and Appendages** | Rash | 16 (7) | 2 (4) | 3 (5) | 9 (15) | 2 (3) |
| | Pruritis | 12 (5) | 2 (4) | 6 (11) | 3 (5) | 1 (2) |
| | Urticaria | 6 (3) | 1 (2) | 2 (4) | 2 (3) | 1 (2) |
| | Sweating | 5 (2) | 2 (4) | 0 | 1 (2) | 2 (3) |
| **Urogenital** | Infection, Urinary Tract | 6 (3) | 2 (4) | 1 (2) | 1 (2) | 2 (3) |
| | Urine abnormality | 4 (2) | 0 | 2 (4) | 1 (2) | 1 (2) |

## 3. Study MA-07

**Table 157: MA-07 Common (≥2%) AEs Incidence by Body System**

| ITT Patients, n = | | By Sept-2001 814 | By Jan-2001 814 |
|---|---|---|---|
| **Body System** | **COSTART Term** | | |
| **Body as a Whole** | All | 432 (53) | 484 (59) |
| | Infection | 169 (21) | 191 (23) |
| | Pain | 104 (13) | 134 (16) |
| | Headache | 82 (10) | 90 (11) |
| | Injury, Accidental | 51 (6) | 58 (7) |
| | Flu Syndrome | 44 (5) | 59 (7) |
| | Asthenia | 43 (5) | 50 (6) |
| | Pain, Abdominal | 40 (5) | 47 (6) |
| | Pain, Back | 39 (5) | 43 (5) |
| | Pain, Chest | 23 (3) | 34 (4) |
| | Fever | 14 (2) | 17 (2) |
| | Pain, Neck | 13 (2) | 15 (2) |
| | Allergic Reaction | 12 (1) | 17 (2) |
| **Cardiovascular** | All | 548 (67) | 572 (70) |
| | Flushing | 499 (61) | 513 (63) |
| | Hypertension | 16 (2) | 20 (2) |
| | Angina Pectoris | 15 (2) | 17 (2) |
| | Palpitations | 13 (2) | 15 (2) |
| | Cardiovascular Disorder | 10 (1) | 18 (2) |
| **Digestive** | All | 249 (31) | 286 (35) |
| | Nausea | 74 (9) | 83 (10) |
| | Diarrhea | 71 (9) | 82 (10) |
| | Dyspepsia | 57 (7) | 62 (8) |
| | Flatulence | 32 (4) | 35 (4) |
| | Vomiting | 32 (4) | 36 (4) |
| | Constipation | 24 (3) | 32 (4) |
| | Gastrointestinal Disorder | 16 (2) | 20 (2) |
| | Abscess, Periodontal | 13 (2) | 14 (2) |
| **Hematologic and Lymphatic** | All | 42 (1) | 52 (6) |
| | Ecchymosis | 16 (2) | 23 (3) |
| **Metabolic and Nutritional** | All | 148 (18) | 175 (21) |
| | Hyperglycemia | 45 (6) | 45 (6) |
| | Edema, Peripheral | 34 (4) | 41 (5) |
| | CPK Increase | 25 (3) | 31 (4) |
| | Glucose Tolerance Decrease | 20 (2) | 22 (3) |
| | Diabetes Mellitus | 13 (2) | 17 (2) |
| **Musculoskeletal** | All | 88 (11) | 112 (14) |
| | Myalgia | 23 (3) | 31 (4) |
| | Cramps, Leg | 18 (2) | 24 (3) |
| | Arthritis | 10 (1) | 13 (2) |
| | Tendon Disorder | 9 (1) | 13 (2) |
| **Nervous** | All | 179 (22) | 208 (26) |
| | Dizziness | 46 (6) | 54 (7) |
| | Paresthesia | 31 (4) | 32 (4) |
| | Insomnia | 26 (3) | 33 (4) |
| | Dry Mouth | 17 (2) | 18 (2) |
| | Depression | 15 (2) | 20 (2) |
| | Anxiety | 11 (1) | 17 (2) |

| | | By Sept-2001 | By Jan-2001 |
|---|---|---|---|
| **Respiratory** | All | 141 (17) | 171 (21) |
| | Sinusitis | 35 (4) | 46 (6) |
| | Rhinitis | 34 (4) | 42 (5) |
| | Cough, Increase | 25 (3) | 33 (4) |
| | Bronchitis | 22 (3) | 29 (4) |
| | Pharyngitis | 20 (2) | 23 (3) |
| | Dyspnea | 13 (2) | 14 (2) |
| **Skin and Appendages** | All | 246 (30) | 271 (33) |
| | Pruritis | 135 (17) | 148 (18) |
| | Rash | 88 (11) | 96 (12) |
| | Skin, Dry | 19 (2) | 21 (3) |
| | Sweating | 12 (1) | 15 (2) |
| **Urogenital** | All | 82 (10) | 100 (12) |
| | Infection, Urinary Tract | 17 (2) | 19 (2) |

## 4. MA-07 Extension Study

**Table 158: MA-07 Common (≥2%) AEs at Jan-2001 and Mar-2001 Updates**

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

| | | Jan-2001 Update | Mar-2001 Update |
|---|---|---|---|
| **Respiratory** | Sinusitis | 46 (6) | 55 (7) |
| | Rhinitis | 42 (5) | 50 (6) |
| | Cough, Increase | 33 (4) | 36 (4) |
| | Bronchitis | 29 (4) | 36 (4) |
| | Pharyngitis | 23 (3) | 29 (4) |
| | Dyspnea | 14 (2) | 21 (3) |
| | Pneumonia | 12 (1) | 15 (2) |
| **Skin and Appendages** | Pruritis | 148 (18) | 154 (19) |
| | Rash | 96 (12) | 105 (13) |
| | Skin, Dry | 21 (3) | 24 (3) |
| | Sweating | 15 (2) | 15 (2) |
| **Urogenital** | Infection, Urinary Tract | 19 (2) | 25 (3) |
| | Prostate disorder | 8 (1) | 14 (2) |

## 5. Study MA-09

**Table 159: MA-09 Common (≥2%) AEs Incidence by Body System**

| | | All | Male | Female | Geriatric | Non-Geriatric |
|---|---|---|---|---|---|---|
| Patients, n = | | 106 | 59 | 47 | 35 | 71 |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | 18 (17) | 11 (19) | 7 (15) | 8 (23) | 10 (14) |
| | Flu syndrome | 10 (9) | 8 (14) | 2 (4) | 1 (3) | 9 (13) |
| | Injury, accidental | 10 (9) | 3 (5) | 7 (15) | 4 (11) | 6 (8) |
| | Pain | 10 (9) | 8 (14) | 2 (4) | 2 (6) | 8 (11) |
| | Pain, abdominal | 8 (8) | 4 (7) | 4 (9) | 4 (11) | 4 (6) |
| | Headache | 6 (6) | 3 (5) | 3 (6) | 1 (3) | 5 (7) |
| | Asthenia | 4 (4) | 1 (2) | 3 (6) | 2 (6) | 2 (3) |
| | Pain, back | 4 (4) | 1 (2) | 3 (6) | 2 (6) | 2 (3) |
| | Allergic reaction | 3 (3) | 3 (5) | 0 | 1 (3) | 2 (3) |
| | Pain, chest | 3 (3) | 1 (2) | 2 (4) | 0 | 3 (4) |
| | Infection, fungal | 2 (2) | 1 (2) | 1 (2) | 0 | 2 (3) |
| **Cardiovascular** | Flushing | 42 (40) | 18 (31) | 25 (53) | 15 (43) | 28 (39) |
| | Cardiovascular disorder | 4 (4) | 2 (3) | 2 (4) | 2 (6) | 2 (3) |
| | Hypertension | 4 (4) | 4 (7) | 0 | 0 | 4 (6) |
| | Coronary artery disorder | 2 (2) | 2 (3) | 0 | 2 (6) | 0 |
| | Vascular disorder | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| | Vein, varicose | 2 (2) | 0 | 2 (4) | 0 | 2 (3) |
| **Digestive** | Diarrhea | 11 (10) | 8 (14) | 3 (6) | 3 (9) | 8 (11) |
| | Dyspepsia | 9 (8) | 5 (8) | 4 (9) | 1 (3) | 8 (11) |
| | Nausea | 9 (8) | 3 (5) | 6 (13) | 4 (11) | 5 (7) |
| | GI disorder | 6 (6) | 3 (5) | 3 (6) | 2 (6) | 4 (6) |
| | Flatulence | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| | Vomiting | 4 (4) | 2 (3) | 2 (4) | 1 (3) | 3 (4) |
| | Abscess, periodontal | 3 (3) | 1 (2) | 2 (4) | 2 (6) | 1 (1) |
| | Ulcer, mouth | 2 (2) | 2 (3) | 0 | 0 | 2 (3) |
| **Hematologic and Lymphatic** | Anemia | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| | Ecchymosis | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| | RBC abnormality | 2 (2) | 2 (3) | 0 | 0 | 2 (3) |
| **Metabolic and Nutritional** | CPK, increased | 5 (5) | 3 (5) | 2 (4) | 1 (3) | 4 (6) |
| | Hyperglycemia | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| | Edema, peripheral | 4 (4) | 2 (3) | 2 (4) | 2 (6) | 2 (3) |
| | Creatinine, increased | 2 (2) | 1 (2) | 1 (2) | 2 (6) | 0 |
| | Edema | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| | Glucose tolerance, decreased | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| | Hyperuricemia | 2 (2) | 0 | 2 (4) | 1 (3) | 1 (1) |
| | SGOT, increased | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| **Musculoskeletal** | Arthritis | 4 (4) | 2 (3) | 2 (4) | 1 (3) | 3 (4) |
| | Cramps, leg | 4 (4) | 0 | 4 (9) | 3 (9) | 1 (1) |
| | Arthralgia | 3 (3) | 2 (3) | 1 (2) | 0 | 3 (4) |
| | Joint disorder | 2 (2) | 1 (2) | 1 (2) | 0 | 2 (3) |
| | Myalgia | 2 (2) | 0 | 2 (4) | 0 | 2 (3) |
| | Tendon disorder | 2 (2) | 2 (3) | 0 | 0 | 2 (3) |

| | | All | Male | Female | Geriatric | Non-Geriatric |
|---|---|---|---|---|---|---|
| **Nervous** | Anxiety | 4 (4) | 2 (3) | 2 (4) | 1 (3) | 3 (4) |
| | Insomnia | 3 (3) | 1 (2) | 2 (4) | 1 (3) | 2 (3) |
| | Dizziness | 2 (2) | 0 | 2 (4) | 2 (6) | 0 |
| | Dry mouth | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| | Hypertonia | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| | Hypesthesia | 2 (2) | 2 (3) | 0 | 0 | 2 (3) |
| **Respiratory** | Sinusitis | 6 ( 6) | 5 (8) | 1 (2) | 1 (3) | 5 (7) |
| | Rhinitis | 5 (5) | 3 (5) | 2 (4) | 0 | 5 (7) |
| | Bronchitis | 4 (4) | 3 (5) | 1 (2) | 0 | 4 (6) |
| | Dyspnea | 2 (2) | 1 (2) | 1 (2) | 0 | 2 (3) |
| | Lung disorder | 2 (2) | 1 (2) | 1 (2) | 2 (6) | 0 |
| **Skin and Appendages** | Pruritis | 11 (10) | 3 (5) | 8 (17) | 6 (17) | 5 (7) |
| | Rash | 8 (8) | 6 (10) | 2 (4) | 3 (9) | 5 (7) |
| | Skin, dry | 6 (6) | 5 (8) | 1 (2) | 1 (3) | 5 (7) |
| | Dermatitis, fungal | 2 (2) | 0 | 2 (4) | 0 | 2 (3) |
| | Hyperpigmentation | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| **Special Senses** | Ear disorder | 2 (2) | 2 (3) | 0 | 1 (3) | 1 (1) |
| | Glaucoma | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| **Urogenital** | Prostate disorder | 4 (4) | 4 (7) | 0 | 1 (3) | 3 (4) |
| | Infection, urinary tract | 3 (3) | 1 (2) | 2 (4) | 0 | 3 (4) |
| | Hematuria | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |
| | Urinary abnormality | 2 (2) | 1 (2) | 1 (2) | 1 (3) | 1 (1) |

## D. Appendix IV: Most Common Adverse Events (≥5% Overall) by Subgroup

### 1. Male vs Female

### a) Study MA-14

**Table 160: MA-14 Most Common AEs (≥5%), 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 |
| **Body System** | **COSTART Term** | M/F | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | M | 10 (12) | 1 (6) | 1 (6) | 4 (22) | 1 (7) | 3 (17) |
| | | F | 14 (18) | 3 (21) | 3 (18) | 0 | 4 (24) | 4 (27) |
| | Asthenia | M | 4 (5) | 1 (6) | 0 | 1 (6) | 1 (7) | 1 (6) |
| | | F | 8 (10) | 2 (14) | 3 (18) | 0 | 1 (6) | 2 (13) |
| | Pain | M | 7 (8) | 2 (12) | 0 | 2 (11) | 1 (7) | 2 (11) |
| | | F | 5 (6) | 1 (7) | 3 (18) | 0 | 0 | 1 (7) |
| | Headache | M | 3 (4) | 0 | 0 | 2 (11) | 0 | 1 (6) |
| | | F | 6 (8) | 3 (21) | 1 (6) | 0 | 1 (6) | 1 (7) |
| | Flu Syndrome | M | 2 (2) | 2 (12) | 0 | 0 | 0 | 0 |
| | | F | 6 (8) | 2 (14) | 1 (6) | 3 (19) | 0 | 0 |
| | Pain, Abdominal | M | 4 (5) | 0 | 0 | 2 (11) | 2 (13) | 0 |
| | | F | 4 (5) | 1 (7) | 0 | 1 (6) | 0 | 2 (13) |
| **Cardiovascular** | Flushing | M | 40 (47) | 11 (65) | 7 (41) | 10 (56) | 10 (67) | 2 (11) |
| | | F | 46 (62) | 9 (64) | 11 (65) | 12 (75) | 11 (65) | 3 (20) |
| **Digestive** | Nausea | M | 2 (2) | 1 (6) | 0 | 1 (6) | 0 | 0 |
| | | F | 12 (15) | 6 (43) | 1 (6) | 1 (6) | 2 (13) | 2 (13) |
| | Diarrhea | M | 6 (7) | 2 (12) | 0 | 3 (17) | 1 (7) | 0 |
| | | F | 6 (8) | 4 (29) | 0 | 1 (6) | 1 (6) | 0 |
| | Vomiting | M | 3 (4) | 2 (12) | 0 | 1 (6) | 0 | 0 |
| | | F | 5 (6) | 2 (14) | 0 | 1 (6) | 2 (13) | 0 |
| **Skin and Appendages** | Pruritis | M | 3 (4) | 0 | 0 | 2 (11) | 0 | 1 (6) |
| | | F | 9 (11) | 4 (29) | 1 (6) | 1 (6) | 2 (13) | 1 (7) |
| | Rash | M | 1 (1) | 0 | 0 | 1 (6) | 0 | 0 |
| | | F | 8 (10) | 2 (14) | 1 (6) | 2 (13) | 2 (13) | 1 (7) |

## b) Study MA-06

**Table 161: MA-06 Most Common AEs (≥5%), 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 |
| **Body System** | **COSTART Term** | M/F | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | M | 32 (25) | 11 (35) | 9 (28) | 5 (18) | 7 (24) |
| | | F | 20 (19) | 6 (23) | 4 (16) | 5 (15) | 5 (23) |
| | Headache | M | 6 (5) | 1 (3) | 2 (6) | 3 (11) | 0 |
| | | F | 22 (21) | 10 (38) | 3 (12) | 6 (18) | 3 (14) |
| | Pain | M | 13 (10) | 2 (6) | 5 (16) | 3 (11) | 3 (10) |
| | | F | 10 (9) | 2 (8) | 3 (12) | 2 (6) | 3 (14) |
| | Flu syndrome | M | 6 (5) | 0 | 3 (9) | 1 (4) | 2 (7) |
| | | F | 9 (8) | 3 (10) | 2 (8) | 2 (6) | 2 (9) |
| | Pain, Back | M | 9 (7) | 5 (16) | 0 | 2 (7) | 2 (7) |
| | | F | 6 (6) | 1 (4) | 0 | 2 (6) | 3 (14) |
| **Cardiovascular** | Flushing | M | 76 (58) | 25 (81) | 26 (81) | 18 (64) | 7 (24) |
| | | F | 72 (68) | 22 (85) | 21 (84) | 24 (73) | 5 (23) |
| **Digestive System** | Nausea | M | 7 (5) | 2 (6) | 3 (9) | 2 (7) | 0 |
| | | F | 6 (6) | 1 (4) | 3 (12) | 2 (6) | 0 |
| | Diarrhea | M | 6 (5) | 3 (10) | 2 (6) | 1 (4) | 0 |
| | | F | 5 (5) | 0 | 2 (8) | 1 (3) | 2 (9) |
| **Skin and Appendages** | Rash | M | 7 (5) | 1 (3) | 1 (3) | 3 (11) | 2 (7) |
| | | F | 9 (8) | 1 (4) | 2 (8) | 6 (18) | 0 |
| | Pruritis | M | 4 (3) | 0 | 2 (6) | 1 (4) | 1 (3) |
| | | F | 8 (8) | 2 (8) | 4 (16) | 2 (6) | 0 |

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## 2. Geriatric vs Non-Geriatric

### a) Study MA-14

**Table 162: MA-14 Most Common AEs (≥5%), 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 |
| **Body System** | **COSTART Term** | G\NG | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | G | 6 (10) | 1 (13) | 1 (7) | 0 | 2 (15) | 2 (15) |
| | | NG | 18 (18) | 3 (13) | 3 (15) | 4 (21) | 3 (16) | 5 (25) |
| | Asthenia | G | 4 (6) | 1 (13) | 2 (14) | 0 | 0 | 1 (8) |
| | | NG | 8 (8) | 2 9) | 1 (5) | 1 (5) | 2 (11) | 2 (10) |
| | Pain | G | 7 (11) | 2 (25) | 2 (14) | 0 | 1 (8) | 2 (15) |
| | | NG | 5 (5) | 1 (4) | 1 (5) | 2 (11) | 0 | 1 (5) |
| | Headache | G | 2 (3) | 0 | 1 (7) | 1 (7) | 0 | 0 |
| | | NG | 7 (7) | 3 (13) | 0 | 1 (5) | 1 (5) | 2 (10) |
| | Flu Syndrome | G | 1 (2) | 0 | 1 (7) | 0 | 0 | 0 |
| | | NG | 7 (7) | 4 (17) | 0 | 3 (16) | 0 | 0 |
| | Pain, abdominal | G | 5 (8) | 1 (13) | 0 | 2 (13) | 1 (8) | 1 (8) |
| | | NG | 3 (3) | 0 | 0 | 1 (5) | 1 (5) | 1 (5) |
| **Cardiovascular** | Flushing | G | 27 (43) | 4 (50) | 6 (43) | 9 (60) | 7 (54) | 1 (8) |
| | | NG | 59 (58) | 16 (70) | 12 (60) | 13 (68) | 14 (74) | 4 (20) |
| **Digestive** | Nausea | G | 5 (8) | 4 (50) | 1 (7) | 0 | 0 | 0 |
| | | NG | 9 (9) | 3 (13) | 0 | 2 (11) | 2 (11) | 2 (10) |
| | Diarrhea | G | 4 (6) | 2 (25) | 0 | 2 (13) | 0 | 0 |
| | | NG | 8 (8) | 4 (17) | 0 | 2 (11) | 2 (11) | 0 |
| | Vomiting | G | 3 (5) | 2 (25) | 0 | 0 | 1 (8) | |
| | | NG | 5 (5) | 2 (9) | 0 | 2 (11) | 1 (5) | 0 |
| **Skin and Appendages** | Pruritis | G | 5 (8) | 1 (13) | 1 (7) | 2 (13) | 0 | 1 (8) |
| | | NG | 7 (7) | 3 (13) | 0 | 1 (5) | 2 (11) | 1 (5) |
| | Rash | G | 6 (10) | 2 (25) | 0 | 2 (13) | 2 (15) | 0 |
| | | NG | 3 (3) | 0 | 1 (5) | 1 (5) | 0 | 1 (5) |

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## b) Study MA-06

**Table 163: MA-06 Most Common AEs (≥5%) , 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 |
| **Body System** | **COSTART Term** | G/NG | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Infection | G | 14 (18) | 2 (11) | 3 (15) | 4 (24) | 5 (20) |
| | | NG | 38 (24) | 15 (38) | 10 (27) | 6 (14) | 7 (19) |
| | Headache | G | 11 (14) | 4 (22) | 3 (15) | 3 (18) | 1 (4) |
| | | NG | 17 (11) | 7 (18) | 2 (5) | 6 (14) | 2 (6) |
| | Pain | G | 9 (11) | 2 (11) | 4 (20) | 0 | 3 (12) |
| | | NG | 14 (9) | 2 (5) | 4 (11) | 5 (11) | 3 (8) |
| | Flu syndrome | G | 3 (4) | 0 | 1 (5) | 1 (6) | 1 (4) |
| | | NG | 12 (8) | 3 (8) | 4 (11) | 2 (5) | 3 (8) |
| | Pain, Back | G | 4 (5) | 2 (11) | 0 | 0 | 2 (8) |
| | | NG | 11 (7) | 4 (10) | 0 | 4 (9) | 3 (8) |
| **Cardiovascular** | Flushing | G | 47 (59) | 13 (72) | 18 (90) | 12 (71) | 4 (16) |
| | | NG | 101 (65) | 34 (87) | 29 (78) | 30 (68) | 8 (22) |
| **Digestive** | Nausea | G | 4 (5) | 1 (6) | 1 (5) | 2 (12) | 0 |
| | | NG | 9 (6) | 2 (5) | 5 (14) | 2 (5) | 0 |
| | Diarrhea | G | 3 (4) | 0 | 2 (10) | 1 (6) | 0 |
| | | NG | 8 (5) | 3 (8) | 2 (5) | 1 (2) | 2 (6) |
| **Skin and Appendages** | Rash | G | 5 (5) | 0 | 2 (10) | 3 (18) | 0 |
| | | NG | 11 (7) | 2 (5) | 1 (3) | 6 (14) | 2 (6) |
| | Pruritis | G | 6 (8) | 1 (6) | 4 (20) | 1 (6) | 0 |
| | | NG | 6 (4) | 1 (3) | 2 (5) | 2 (5) | 1 (3) |

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## E. Appendix V: Discontinuations Due to Adverse Events

### 1. Study MA-14

**Table 164: MA-14 Discontinuations Due to Adverse Events, All Reported Terms**

| | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | All | Niaspan | Advi/10 | Advi/20 | Advi/40 | Lovastatin |
| Randomized Patients, n = | | 164 | 31 | 34 | 34 | 32 | 33 |
| All Discontinuations, n (%) | | 35(21) | 8(26) | 4(12) | 10(29) | 9(28) | 4(12) |
| Discontinued for AE*, n (%) | | 28(17) | 7(23) | 2 (6) | 9 (26) | 7 (22) | 3 (9) |
| **Body as a Whole** | Asthenia | 3 (2) | 1 (3) | 0 | 0 | 1 (3) | 1 (3) |
| | Headache | 2 (1) | 1 (3) | 0 | 0 | 0 | 1 (3) |
| | Pain, abdominal | 1 (1) | 0 | 0 | 0 | 0 | 1 (3) |
| **Cardiovascular** | Flushing | 9 (5) | 3 (10) | 0 | 4 (12) | 2 (6) | 0 |
| | Syncope | 2 (1) | 0 | 0 | 1 (3) | 1 (3) | 0 |
| | Palpitations | 1 (1) | 0 | 0 | 0 | 0 | 1 (3) |
| **Digestive** | Nausea | 3 (2) | 1 (3) | 0 | 0 | 1 (3) | 1 (3) |
| | Diarrhea | 2 (1) | 1 (3) | 0 | 0 | 1 (3) | 0 |
| | Vomiting | 2 (1) | 2 (6) | 0 | 0 | 0 | 0 |
| | Gastroenteritis | 1 (1) | 0 | 0 | 1 (3) | 0 | 0 |
| **Metabolic and Nutritional** | Edema | 1 (1) | 0 | 1 (3) | 0 | 0 | 0 |
| **Skin and Appendages** | Rash | 7 (4) | 1 (3) | 1 (3) | 3 (9) | 2 (6) | 0 |
| | Pruritis | 3 (2) | 0 | 0 | 1 (3) | 2 (6) | 0 |
| | Urticaria | 3 (2) | 0 | 0 | 3 (9) | 0 | 0 |
| | Alopecia | 2 (1) | 0 | 0 | 1 (3) | 0 | 1 (3) |
| **Special Senses** | Amblyopia | 1 (1) | 0 | 0 | 0 | 0 | 1 (3) |
| | Vision Abnormality | 1 (1) | 0 | 0 | 0 | 0 | 1 (3) |
| **Urogenital** | Infection, urinary tract | 1 (1) | 0 | 0 | 1 (3) | 0 | 0 |

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

## 2. Study MA-06

**Table 165: MA-06 Discontinuations Due to Adverse Events, All Reported Terms**

| | | | Treatment | | | |
|---|---|---|---|---|---|---|
| | | **All** | **Advi/20** | **Advi/40** | **Niaspan** | **lovastatin** |
| ITT Patients, n = | | 236 | 57 | 57 | 61 | 61 |
| All Discontinuations, n (%) | | 60 (25) | 17 (30) | 15 (26) | 20 (33) | 8 (13) |
| Discontinued for AE*, n (%) | | 40 (17) | 12 (21) | 10 (18) | 12 (20) | 6 (10) |
| **Body as a Whole** | Asthenia | 2 (1) | 0 | 1 (2) | 1 (2) | 0 |
| | Headache | 4 (2) | 1 (2) | 1 (2) | 2 (3) | 0 |
| | Pain, abdominal | 2 (1) | 1 (2) | 1 (2) | 0 | 0 |
| | Pain | 1 (<1) | 0 | 0 | 1 (2) | 0 |
| **Cardiovascular** | Flushing | 16 (7) | 6 (11) | 6 (11) | 3 (5) | 1 (2) |
| | Infarction, Myocardial | 1 (<1) | 1 (2) | 0 | 0 | 0 |
| **Digestive** | Nausea | 1 (<1) | 0 | 1 (2) | 0 | 0 |
| | Vomiting | 1 (<1) | 0 | 1 (2) | 0 | 0 |
| | Diarrhea, Bloody | 1 (<1) | 1 (2) | 0 | 0 | 0 |
| **Metabolic and Nutritional** | Edema | 3 (1) | 1 (2) | 1 (2) | 0 | 1 (2) |
| | Hyperglycemia | 2 (1) | 1 (2) | 0 | 0 | 1 (2) |
| **Musculoskeletal** | Myalgia | 8 (3) | 2 (4) | 0 | 2 (3) | 4 (7) |
| **Nervous** | Insomnia | 1 (<1) | 1 (2) | 0 | 0 | 0 |
| | Paresthesias | 3 (1) | 1 (2) | 0 | 2 (3) | 0 |
| | Twitch | 1 (<1) | 0 | 0 | 1 (2) | 0 |
| | Hypertonia | 1 (<1) | 0 | 0 | 1 (2) | 0 |
| **Skin and Appendages** | Rash | 6 (3) | 1 (2) | 1 (2) | 3 (5) | 1 (2) |
| | Pruritis | 6 (3) | 1 (2) | 2 (4) | 2 (3) | 1 (2) |
| | Urticaria | 4 (2) | 0 | 1 (2) | 2 (3) | 1 (2) |
| **Special Senses** | Vision Abnormality | 1 (<1) | 0 | 1 (2) | 0 | 0 |

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

## 3. Study MA-07

**Table 166: MA-07 All Discontinuations for Adverse Events, Overall and by Subgroup**

| | | | Subgroup | | | |
|---|---|---|---|---|---|---|
| | | **ITT, All** | **Male** | **Female** | **Geriatric** | **Non-Geriatric** |
| **ITT Patients, n =** | | 814 | 518 | 296 | 296 | 518 |
| **All Discontinuations, n (%)** | | 264 (32) | 140 (27) | 124 (42) | 111 (38) | 153 (30) |
| **Discontinued for AE*, n (%)** | | 188 (23) | 91 (18) | 97 (33) | 90 (30) | 98 (19) |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Headache | 10 (1) | 4 (1) | 6 (2) | 4 (1) | 6 (1) |
| | Pain, abdominal | 9 (1) | 4 (1) | 5 (2) | 4 (1) | 5 (1) |
| | Pain | 6 (1) | 1 (<1) | 5 (2) | 3 (1) | 3 (1) |
| | Asthenia | 4 (<1) | 1 (<1) | 3 (1) | 1 (<1) | 3 (1) |
| | Pain, chest | 3 (<1) | 1 (<1) | 2 (1) | 0 | 3 (1) |
| | Hernia | 2 (<1) | 0 | 2 (1) | 1 (<1) | 1 (<1) |
| | Carcinoma | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Edema, face | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Fever | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Malaise | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Pain, back | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Photosensitivity | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| **Cardiovascular** | Flushing | 79 (10) | 39 (8) | 40 (14) | 29 (10) | 50 (10) |
| | Palpitations | 4 (<1) | 2 (<1) | 2 (1) | 0 | 4 (1) |
| | Occlusion, coronary | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) |
| | Syncope | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | Fibrillation, atrial | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Flutter, atrial | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| **Digestive** | Diarrhea | 12 (1) | 3 (1) | 9 (3) | 7 (2) | 5 (1) |
| | Nausea | 11 (1) | 1 (<1) | 10 (3) | 3 (1) | 8 (2) |
| | Dyspepsia | 5 (1) | 1 (<1) | 4 (1) | 2 (1) | 3 (1) |
| | Vomiting | 5 (1) | 0 | 5 (2) | 1 (<1) | 4 (1) |
| | Constipation | 3 (<1) | 1 (<1) | 2 (1) | 1 (<1) | 2 (<1) |
| | Esophagitis | 2 (<1) | 0 | 2 (1) | 1 (<1) | 1 (<1) |
| | Flatulence | 2 (<1) | 1 (<1) | 1 (<1) | 0 | 2 (<1) |
| | Stool abnormality | 2 (<1) | 0 | 2 (1) | 2 (1) | 0 |
| | Dysphagia | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Gastritis | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | GI disorder | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Hemorrhage, GI | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Hepatitis C | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Liver function abnormality | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Rectal disorder | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| | Ulcer, peptic | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Ulcer, stomach | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |

| | | ITT, All | Male | Female | Geriatric | Non-Geriatric |
|---|---|---|---|---|---|---|
| **Hematologic and Lymphatic** | Thrombocytopenia | 3 (<1) | 3 (1) | 0 | 1 (<1) | 2 (<1) |
| | Platelets decreased | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| **Metabolic and Nutritional** | Hyperglycemia | 8 (1) | 6 (1) | 2 (1) | 0 | 8 (2) |
| | CPK Increased | 7 (1) | 7 (1) | 0 | 2 (1) | 5 (1) |
| | Glucose tolerance decreased | 5 (1) | 5 (1) | 0 | 3 (1) | 2 (<1) |
| | Edema, peripheral | 4 (<1) | 1 (<1) | 3 (1) | 2 (1) | 2 (<1) |
| | Edema | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | SGOT Increased | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | SGPT Increased | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | Bilirubinemia | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Diabetes Mellitus | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Gout | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Hyponatremia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Thirst | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Weight Decrease | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| **Musculoskeletal** | Cramps, leg | 4 (<1) | 0 | 4 (1) | 2 (1) | 2 (<1) |
| | Myasthenia | 3 (<1) | 0 | 3 (1) | 2 (1) | 1 (<1) |
| | Myalgia | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | Arthralgia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Myopathy | 1 (<1) | 0 | 1 (<1) | 0 | 1 (<1) |
| **Nervous** | Dizziness | 3 (<1) | 0 | 3 (1) | 1 (<1) | 2 (<1) |
| | Insomnia | 3 (<1) | 0 | 3 (1) | 0 | 3 (1) |
| | Dry mouth | 2 (<1) | 2 (<1) | 0 | 1 (<1) | 1 (<1) |
| | Nervousness | 2 (<1) | 0 | 2 (1) | 0 | 2 (<1) |
| | Tremor | 2 (<1) | 0 | 2 (1) | 0 | 2 (<1) |
| | Amnesia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Anxiety | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Depression | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Dream abnormality | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Emotional lability | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Hypertonia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Hypesthesia | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Paresthesia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Somnolence | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Thinking abnormality | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| **Respiratory** | Dyspnea | 2 (<1) | 1 (<1) | 1 (<1) | 1 (<1) | 1 (<1) |
| | Asthma | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Cough increased | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Laryngismus | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| | Lung disorder | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Pharyngitis | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Voice alteration | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |

| | | ITT, All | Male | Female | Geriatric | Non-Geriatric |
|---|---|---|---|---|---|---|
| **Skin and Appendages** | Pruritis | 33 (4) | 18 (3) | 15 (5) | 20 (4) | 13 (4) |
| | Rash | 20 (2) | 8 (2) | 12 (4) | 12 (4) | 8 (2) |
| | Urticaria | 8 (1) | 4 (1) | 4 (1) | 4 (1) | 4 (1) |
| | Psoriasis | 2 (<1) | 2 (<1) | 0 | 2 (1) | 0 |
| | Skin discoloration | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) |
| | Herpes zoster | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Hypertrophy, skin | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Rash, petechial | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Skin disorder | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 |
| **Special Senses** | Amblyopia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) |
| | Tinnitus | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| **Urogenital** | Carcinoma, bladder | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |
| | Carcinoma, prostate | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 0 |

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

## 4. Study MA-07, 48-Week Extension

**Table 167: 48-Week Extension Study Discontinuations Due to Adverse Events, Overall and by Subgroups**

| | | | Subgroup | | | |
|---|---|---|---|---|---|---|
| | | **All** | **Male** | **Female** | **Geriatric** | **Non-Geriatric** |
| **Patients, n =** | | 300 | 205 | 95 | 110 | 190 |
| **All Discontinuations, n (%)** | | 47 (16) | 27 | 20 | 20 | 27 |
| **Discontinued for AE*, n (%)** | | 30 (10) | 15 | 15 | 15 | 15 |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Allergic reaction | 1 (<1) | 1 (<1) | 0 | 1 (1) | 0 |
| | Pain | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| | Pain, back | 1 (<1) | 1 (<1) | 0 | 1 (1) | 0 |
| **Cardiovascular** | Flushing | 8 (3) | 3 (1) | 5 (5) | 5 (5) | 3 (2) |
| | Heart Arrest | 2 (1) | 1 (<1) | 1 (1) | 1 (1) | 1 (1) |
| | Anomaly, vascular | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | Cardiovascular disorder | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | Hemorrhaging | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | Infarction, myocardial | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | Palpitations | 1 (<1) | 0 | 1 (1) | 0 | 1 (1) |
| **Digestive** | Diarrhea | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| | Colitis | 2 (1) | 1 (<1) | 1 (1) | 2 (2) | 0 |
| | Constipation | 1 (<1) | 1 (<1) | 0 | 1 (1) | 0 |
| | Gastric hemorrhage | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | GI disorder | 1 (<1) | 0 | 1 (1) | 0 | 1 (1) |
| | Hepatitis | 1 (<1) | 1 (<1) | 0 | 1 (1) | 0 |
| | Rectal disorder | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| | Ulcer duodenal perforated | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| | Vomiting | 2 (1) | 1 (<1) | 1 (1) | 0 | 2 (1) |
| | Nausea | 4 (1) | 0 | 4 (4) | 2 (2) | 2 (1) |
| **Metabolic and Nutritional** | CPK increased | 2 (1) | 2 (1) | 0 | 0 | 2 (1) |
| | Glucose tolerance decreased | 2 (1) | 1 (<1) | 1 (1) | 1 (1) | 1 (1) |
| | Hyperglycemia | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| **Musculoskeletal** | Cramps, leg | 1 (<1) | 0 | 1 (1) | 0 | 1 (1) |
| | Tendon disorder | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| **Nervous** | Nervousness | 1 (<1) | 0 | 1 (1) | 0 | 1 (1) |
| **Respiratory** | Dyspnea | 1 (<1) | 0 | 1 (1) | 0 | 1 (1) |
| **Skin and Appendages** | Pruritis | 2 (1) | 0 | 2 (2) | 2 (2) | 0 |
| | Rash | 1 (<1) | 0 | 1 (1) | 1 (1) | 0 |
| | Dermatitis, fungal | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| **Urogenital** | Sexual function abnormality | 1 (<1) | 1 (<1) | 0 | 0 | 1 (1) |
| **Discontinued for Lab Abnormality** | | 3 (1) | 2 (1) | 1 (1) | 1 (1) | 2 (1) |

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

## 5. Study MA-09

**Table 168: MA-09 Discontinuations Due to Adverse Events, Overall and by Subgroup**

| | | | Subgroup | | | |
|---|---|---|---|---|---|---|
| | | All | Male | Female | Geriatric | Non-Geriatric |
| **Patients, n =** | | 106 | 59 | 47 | 35 | 71 |
| **All Discontinuations, n (%)** | | 38 (36) | 18 (31) | 20 (43) | 12 (34) | 26 (37) |
| **Discontinued for AE*, n (%)** | | 30 (28) | 14 (24) | 16 (34) | 11 (31) | 19 (27) |
| **Body System** | **COSTART Term** | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a Whole** | Allergic reaction | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| | Infection, bacterial | 1 (3) | 1 (2) | 0 | 0 | 1 (1) |
| | Pain, abdominal | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| | Pain, chest | 1 (3) | 0 | 1 (2) | 1 (3) | 0 |
| **Cardiovascular** | Flushing | 11 (37) | 3 (5) | 8 (17) | 4 (11) | 7 (10) |
| **Digestive** | Diarrhea | 4 (13) | 2 (3) | 2 (4) | 4 (11) | 0 |
| | Dyspepsia | 4 (13) | 1 (2) | 3 (6) | 3 (9) | 1 (1) |
| | Flatulence | 2 (7) | 0 | 2 (4) | 2 (6) | 0 |
| | Appetite increase | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| | GI disorder | 1 (3) | 0 | 1 (2) | 1 (3) | 0 |
| | Nausea | 1 (3) | 1 (2) | 0 | 0 | 1 (1) |
| | Stomatitis | 1 (3) | 0 | 1 (2) | 1 (3) | 0 |
| **Hematologic and** | Anemia, hypochromic | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| **Lymphatic** | Anemia, macrocytic | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| **Metabolic and** | CPK increase | 7 (23) | 4 (7) | 3 (6) | 6 (17) | 1 (1) |
| **Nutritional** | Hyperuricemia | 4 (13) | 0 | 4 (9) | 2 (6) | 2 (3) |
| | Hyperglycemia | 3 (10) | 1 (2) | 2 (4) | 3 (9) | 0 |
| | SGOT increase | 2 (7) | 2 (3) | 0 | 2 (6) | 0 |
| | SGPT increase | 2 (7) | 2 (3) | 0 | 2 (6) | 0 |
| **Musculoskeletal** | Myalgia | 2 (7) | 0 | 2 (4) | 2 (6) | 0 |
| | Arthralgia | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| | Osteomyelitis | 1 (3) | 1 (2) | 0 | 0 | 1 (1) |
| **Nervous** | Dry mouth | 2 (7) | 2 (3) | 0 | 0 | 2 (3) |
| **Skin and** | Pruritis | 4 (13) | 1 (2) | 3 (6) | 3 (9) | 1 (1) |
| **Appendages** | Rash | 3 (10) | 0 | 3 (6) | 1 (3) | 2 (3) |
| | Herpes zoster | 1 (3) | 0 | 1 (2) | 1 (3) | 0 |
| | Urticaria | 1 (3) | 1 (2) | 0 | 1 (3) | 0 |
| **Discontinued for Lab abnormality** | | 6 (6) | 3 (5) | 3 (6) | 2 (6) | 4 (6) |

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