Department of Veterans Affairs
Veterans Health Administration
Pharmacy Benefits Management Strategic Healthcare Group

August 31, 1999

VHA's Pharmacy Benefits Management Strategic Health Group (PBM) and Medical Advisory Panel (MAP)'s

Niacin Product Selection Workgroup

consisted of previous PBM Hyperlipidemia Guideline reviewers, Lipid Clinic clinicians, and authors of previous niacin guidance:

J. Chris Bradberry, Pharm D.
College of Pharmacy
The University of Tennessee, Memphis

Mark Britton, Pharm D.
College of Pharmacy
The University of Oklahoma

Chris Chandler, Pharm D.
VA Pharmacy Benefits Management
Hines IL

Janet Dailey, Pharm D.
VAMC Alabama

Angeliki Georgopoulos M.D.
Endorinologist, Minneapolis VAMC

David Gray, Pharm D.
VAMC Long Beach, CA

John Guyton, M.D.
Duke University Medical Center

M. Kashyap M.D.
VAMC Long Beach, CA

Alexander Shephard, M.D.
PBM-MAP Member
San Antonio VAMC

VETERANS ADMINISTRATION NIACIN PRODUCT SELECTION

I. Introduction

Niacin is indicated for the treatment of Frederickson Types IIa, IIb, IV and V dyslipidemia. In the Coronary Drug Project, patients who were initially treated with niacin exhibited a reduced risk of recurrent myocardial infarction.[1] In addition to its favorable effect on patient outcomes and low acquisition cost, niacin is also the only agent that decreases lipoprotein(a) in addition to decreasing low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and increasing high-density lipoprotein cholesterol (HDL-C).

Niacin product selection is based on efficacy, safety, and patient tolerability. Niacin is marketed both as Food and Drug Administration (FDA) approved prescription products, and non-FDA approved over-the-counter (OTC) food supplements. At a minimum, products should meet the United States Pharmacopeia (USP) standards of containing 90-110% of the labeled niacin product and have a disintegration time of 30 minutes[2] to assure efficacy and safety.

II. Niacin Immediate Release (IR)

A. Efficacy

Niacin IR is generally more effective than other niacin products for increasing HDL-C.[3] The extent of the lipid reductions vary due to differing baseline levels. Niacin IR should be initiated slowly, with a maximum daily dose of 3gm.

1. Niacin IR (OTC product, Rugby Laboratories) at a dose of 2-3gm/day decreased LDL-C 16-22%, TG 39-42%, and increased HDL-C 31-35%.[3]

2. Niacin IR (prescription product- Nicolar®, Rhone-Poulenc Rorer) at a dose up to 3gm/day decreased LDL-C 28%, TG 38%, and increased HDL–C 22%.[4] In an additional study, Nicolar® at a dose up to 3gm/day decreased LDL-C 25%, TG 26%, and increased HDL-C 36%.[5] In a third study, Nicolar® at an average dose of 2.25 gm/day decreased LDL-C 16%, TG 29%, and increased HDL–C 27%.[6]

3. Niacin IR (OTC product, Goldline Laboratories) at a dose of 3gm/day decreased LDL-C 2%, TG 29%, and increased HDL-C 25%.[7]

4. Niacin IR (Kos Pharmaceuticals product manufactured for research purposes only) at a dose of 1.5-3gm/day decreased LDL-C 13-21%, TG 19-24%, and increased HDL-C 10-24%.[8]

B. Safety and Patient Tolerability

1. The major adverse effect limiting the acceptance of niacin IR therapy is flushing. Other reported effects include nausea, hypotension, tachycardia, increased serum blood glucose and increased uric acid levels.[9]

   Tolerance usually develops to flushing and can be minimized by the use of aspirin (325 mg) or other non-steroidal anti-inflammatory agents, taking it with food, or a reduction in dose.[9]

2. Elevated liver function tests (LFTs), reported as aspartate aminotransferase (AST) and alanine

aminotransferase (ALT) have occurred during niacin IR therapy.[10-11, 12-13] Cholestatic jaundice,[14] generalized synthetic hepatic dysfunction,[15] and fulminant hepatic failure (3gm/day)[16] have also been reported. Alterations in LFTs usually occur within the first 3 to 6 months of therapy at a dose of ≥ 3-4.5 gm/day[10, 12] of niacin IR; however elevations have occurred at doses as low as 0.5gm/day[10] or as long as 10 years after therapy was started.[17]

Based on the niacin product selected, clinicians should weigh the risk for hepatotoxicity for niacin versus the benefits of other lipid lowering agents. Elevated LFTs have been reported to occur when the dose has been increased rapidly. Niacin therapy should be started slowly at ≤ 300 mg/day in divided doses, and increased by ≤ 300 mg/day subsequently each week to a maximum dose of 3 gm/day. Monitoring of LFTs (AST, ALT) should occur at baseline, 6 weeks after initiating therapy or changing the dose, and every 6-12 months thereafter. Clinically significant elevations occur when LFTs rise greater than three times the upper limit of normal (> 3x ULN). Elevated LFTs are usually reversible upon discontinuation, although may lead to hepatotoxicity.[10] Three of the niacin IR products (OTC product, Rugby Laboratories, OTC product, Goldline Laboratories, and prescription product Nicolar®, Rhone-Poulenc Rorer) have published clinical safety data.[3-7] The remaining published studies of niacin IR do not specify which manufacturer or product was used.[1, 18-19, 20-21, 22-23, 24-25, 26-27]

a) Forty-six patients enrolled in a 30 week trial of niacin IR (OTC product, Rugby Laboratories) versus niacin SR (OTC product, Goldline Laboratories).[3] At a dose up to 3gm/day for 30 weeks, niacin IR showed no significant change in LFTs from baseline. Thirty-nine percent of patients taking niacin IR dropped out before completing the 3gm/day regimen due to intolerable flushing, rash, or other adverse effects (significantly less than niacin SR).

b) Seventy-one patients enrolled in a 6 month trial of niacin IR (prescription product-Nicolar®, Rhone-Poulenc Rorer) versus niacin SR (OTC product Nicobid®, Armour Pharmaceuticals).[4] At a dose up to 3gm/day, niacin IR showed no significant changes in LFTs from baseline (AST only, ALT not reported). Over 21% of niacin IR patients dropped out due to intolerable flushing pruritus, elevated LFTs, or other adverse events (no significant difference versus niacin SR). In a second trial, one hundred thirty-six patients enrolled in a 26 week trial of Nicolar® 0.75-4.5gm/day versus lovastatin.[6] One patient (1.5%) taking niacin 4.5gm/day experienced a rise in LFTs from baseline (ALT > 3x ULN), although the mean LFT changes from baseline were not clinically significant. Twenty-two percent of patients in the niacin IR group withdrew due to flushing, pruritus, rash, GI complaints or other adverse effects. The overall discontinuation rates were not significantly different from lovastatin.[5] In a third trial, seventy-four patients enrolled in a 15 week trial of Nicolar® at a dose of up to 3 gm/day, fluvastatin, or the two in combination. In the niacin IR monotherapy group 8.3% experienced LFT (AST) elevations compared to 15.8% in the fluvastatin monotherapy group and 29% in the combination group (although none were > 3x ULN). Sixteen percent of the patients on niacin IR monotherapy or in combination withdrew mainly due to unspecified adverse effects.[5]

c) One hundred-eight patients were enrolled in a 12 week trial of niacin IR (OTC product, Goldline Laboratories) at a dose of 3gm/day versus atorvastatin. No clinically significant LFT abnormalities were noted.[7] Approximately 16% of patients on niacin IR and 2% on atorvastatin withdrew due to unspecified adverse events (significance unreported).

C. Conclusion

1. **Niacin IR is effective in the treatment of dyslipidemia, however the product selected requires adequate safety data.**

2. **Niacin IR (prescription product-Nicolar â, Rhone-Poulenc Rorer) has published safety data, although this product is no longer manufactured.**

3. **Of the OTC products, niacin IR (OTC product, Rugby Laboratories) and (OTC product, Goldline Laboratories) are the only products with published clinical trial data.[3,7] Both are manufactured by multiple sources that all meet USP standards[28,29], although neither collect safety data on their OTC nutritional supplements.**

4. **Currently, only one prescription niacin IR product (Niacor â, Upsher Smith) is available. Although it does not have published safety data, over the past 2 years approximately 1000 prescriptions of Niacor â have been dispensed and to date, the manufacturer has not received a case report of hepatotoxicity.[30]**

5. **Niacin IR (prescription product- Niacor â, Upsher Smith) is the niacin IR product of choice due to its proven efficacy and safety in the treatment of dyslipidemia and should be available in 100 mg, 250 mg, and 500mg strength tablets.**

III. Niacin Sustained Release (SR) and Extended Release (ER)

Niacin ER and SR gradually release niacin over at least 8-12 hours to decrease the incidence of flushing seen with niacin IR.

A. Efficacy

1. Niacin SR (OTC)

Niacin SR is generally more effective at decreasing LDL-C than niacin IR, although less effective at increasing HDL-C.[3] The variability of the lipid reductions is due to differing baseline levels. Niacin SR should be initiated at approximately one-half of the niacin IR dose; the maximum daily dose is 2gm.

a) Niacin SR (OTC product, Goldline Laboratories) at a dose of 1.5-2gm/day reduced LDL-C 22%-33%, TG 25-30%, and increased HDL-C 13%-17%.[3]

b) Niacin SR (OTC product Nicobid®, Armour Pharmaceuticals) at a dose of 3gm/day reduced LDL-C 17%, TG 2%, and increased HDL-C 8%.[4] In another study, Nicobid® at a dose of 1-2gm/day reduced LDL-C 16%, TG 11%, and increased HDL-C 12%.[31]

c) Niacin SR (OTC product Slo-Niacin®, Upsher-Smith) at a dose of 1gm/day reduced LDL-C 18%, TG 29%, and increased HDL-C 16%.[32] In a retrospective study, Slo-Niacin® at an average daily dose of 1.5 gm, reduced LDL-C 24%, TG 33%, and increased HDL-C 6%.[33]

d) Niacin SR (OTC product Endur-acin®, Endurance Products Corporation) at a dose of 1.5gm/day reduced LDL 16% and increased TG 4% and HDL-C < 1%.[34] In another study, Endur-acin® at a dose of 1.5-2gm/day reduced LDL-C 15-22%, TG 10-25%, and increased HDL-C 9-16%.[35] The same study examined differences between younger (20-49 years old) and older (50-70 year old) patients. At a dose of 1.5-2gm/day LDL-C was reduced 29%, TG 21%, and HDL-C was increased 8% in older patients; in younger patients LDL-C was reduced 16%, TG increased <1% and HDL-C increased 7%.[36] In a third study, Endur-acin®at a dose of 1.5-2gm/day reduced LDL-C 20-26%, TG 9-11%, and increased HDL-C 4-9%.[37]

e) Niacin SR (OTC product, Rugby Inc.) at a dose of 1.2gm/day reduced LDL-C 6%, and increased TG 11% and HDL-C 2%.[38]

2. Niacin ER (prescription product-Niaspanâ, Kos Pharmaceuticals)

Niacin ER (prescription product- Niaspan®, Kos Pharmaceuticals) has equivalent daily dosing and similar efficacy to niacin IR[8]. Patients should initiate therapy with the dosing starter pack (Niaspan® 375mg, 500mg, and 750mg tablets, each at bedtime for one week and increase ≤ 500mg in a four week period).[39]

a) Niacin ER (prescription product-Niaspan®, Kos Pharmaceuticals) at a dose of 1.5gm at bedtime reduced LDL-C 13%, TG 10%, and increased HDL-C 19%.[8] In a second study, Niaspan® up to 3 gm at bedtime reduced LDL-C 18%, TG 26%, and increased HDL-C 32%.[40] The third study examined Niaspan® at a dose of 1-2gm/day at bedtime reduced LDL-C 6-15%, TG 21-28%, and increased HDL-C 17-23%.[41]

B. Safety and Patient Tolerability

Niacin therapy should be started slowly at ≤ 250-500 mg/day. Elevated LFTs have occurred when the dose is titrated quickly. Liver function tests (AST, ALT) should be monitored at baseline, 6 weeks after starting therapy or changing of the dose and every 6-12 months thereafter. Clinically significant elevations occur when LFTs > 3x ULN, usually at a dose of ≥ 2 gm/day of niacin SR. Liver function test elevations are usually reversible upon discontinuation, although may lead to hepatotoxicity. Cases of elevated LFTs have been reported when patients taking niacin IR are switched to a mg equivalent dose of niacin SR.[10, 42- 43, 44-45]

1. **Niacin SR (OTC)**

a) The major adverse effects of niacin SR include GI upset and pruritus, which frequently limit patient acceptance.[9] Other reported effects are jaundice, nausea, hypotension, vomiting, tachycardia, increased serum glucose, and increased serum uric acid levels.[9]

b) Based on the niacin product selected, clinicians should weigh the risk for hepatotoxicity for niacin versus the benefits of other lipid lowering agents. Elevated LFTs in patients taking 1.5-6 gm/day of niacin SR (OTC products) have been reported.[10, 42, 46-47] Furthermore, cases of fulminant hepatic failure (6gm/day) and a death (2gm/day) have been reported when taking niacin SR.[48-49]

(1) Forty-six patients were enrolled in a 36 week trial of niacin SR (OTC product, Goldline Laboratories) versus niacin IR (OTC product, Rugby Laboratories) up to 3gm/day.[3] Elevations of LFTs > 3x ULN occurred in 52% of niacin SR patients. Seventy-eight percent of the niacin SR patients dropped out before completing the 3gm/day regimen due to elevated LFTs, GI complaints, or other adverse events. There were no withdrawals due to intolerable flushing, although overall discontinuation rates were significantly higher than with niacin IR.

(2) Seventy-one patients were enrolled in a 26 week trial with niacin SR (OTC product-Nicobid®, SR, Armour Pharmaceuticals) versus niacin IR (prescription product Nicolar®, Rhone-Poulenc Rorer) up to 3 gm/day.[4] No significant changes occurred in LFTs (AST only, ALT values were not reported). Eighteen percent of patients in the niacin SR group dropped out for the following reasons: weight gain and nausea, flushing, chest pain, or headache (no significant difference versus niacin IR).

(3) Twenty-nine patients were enrolled in a 12 week trial of niacin SR (OTC product Slo-Niacin®, Upsher-Smith) 1gm/day or niacin SR plus etofibrate. There were no changes in LFTs or drop-outs due to adverse events.[32] In a retrospective study, 969 medical records for a 3 year period were reviewed. [33] Slo-Niacin® at average daily dose of 1.5gm exhibited mean increases in LFTs that were statistically, but not clinically significant (< 3x ULN). Over 5% of patients had elevated LFTs; 91% were graded as possible, probable, or definitely related to niacin. At 36 months of therapy, approximately 49% of patients discontinued niacin SR therapy; the most common reasons for discontinuation were itching and flushing, increased blood glucose levels, GI symptoms, or elevated LFTs.

(4) Ninety-eight patients were enrolled in 38 week trial of niacin SR (OTC product Endur-acin®, Endurance Products Corporation) at a dose of 1.5gm/day versus diet, oat bran alone, or the oat bran and niacin in combination. Eight percent of the niacin SR patients had LFTs elevated 2 or more standard deviations from the mean (AST, ALT not reported). Twelve percent of patients dropped out for intolerable side effects.[34] In another trial, 89 patients were enrolled in a 6 month trial of Endur-acin (1.5 or 2 gm/day) or placebo for 2 month each. There were no reports of LFTs > 3x ULN; 4.5% of patients dropped out due to medication intolerance.[35] In a third trial, 201 subjects were enrolled in a 26 week trial that compared Endur-acin® 1- 2 gm/day, placebo, and diet alone. One subject (<1%) developed a hepatitis-like syndrome. Abnormal LFTs (AST, ALT not reported) occurred in 4% of patients in the niacin SR group versus 7% of control patients (not significant). Over 3% of patients dropped out due niacin SR side effects.[34,36]

(5) One hundred fifty-eight subjects were enrolled in a 96 week trial that compared niacin SR (OTC product Nicobid[â], Rorer Pharmaceuticals) at a dose of 1-2gm/day, placebo, pravastatin, and the combination of pravastatin and niacin SR. Over 12% of patients experienced LFTs >3 ULN in the niacin SR group. During the first 8 weeks 10% of patients dropped out of the niacin group due to flushing, nausea, or other adverse effects.[31]

(6) Twenty-five patients were enrolled in a 16 month trial of niacin SR (OTC product, Rugby Inc) 1.2gm/day, lovastatin, or the two in combination. No significant LFT abnormalities occurred, although patient withdrawals due to adverse events were not reported. [38]

2. **Niacin ER (prescription product-Niaspan[â], Kos Pharmaceuticals)**

a) Flushing, headache, nausea, and gastrointestinal symptoms were the most common adverse events reported for Niacin ER (prescription product-Niaspan®, Kos Pharmaceuticals) from the combined results of 3 trials.[39] The incidence of flushing is less than reported with Niacin IR (Niaspan®, Kos Pharmaceuticals) 1.5gm/day with 1.88 episodes/month versus niacin IR (Kos Pharmaceuticals product manufactured for research purposes only) 1.5 gm/day with 8.56 flushing episodes/month.[39] The ability to dose Niaspan® once-daily at bedtime may improve patient tolerance to flushing and improve patient compliance.

b) Elevated LFTs have been reported in 1-2% of niacin ER patients.[39] These elevations are usually reversible, although may lead to hepatotoxicity.

(1) Two hundred and thirty-three patients enrolled in a 25 week trial of niacin ER (prescription product-Niaspan®, Kos Pharmaceuticals) 1.5gm at bedtime, niacin IR (Kos Pharmaceuticals product manufactured for research purposes only) 1.5 or 3 gm/day, or placebo.[8] Three percent of patients in the niacin ER group experienced LFTs > 2x ULN and one patient (1.3%) experienced LFTs > 3x ULN (no significant difference). Eleven percent of niacin ER patients withdrew versus 16% in the niacin IR (Kos Pharmaceuticals product manufactured for research purposes only) group (no significant difference).

(2) Two hundred sixty-nine patients enrolled in a 96 week trial of niacin ER (prescription product-Niaspan®, Kos Pharmaceuticals) up to 3 gm at bedtime or in combination with other lipid lowering therapy. Overall, 2% of patients experienced LFTs > 2x ULN in the niacin ER group versus 6 % in the combination therapy group (no significant difference). Fifteen percent of patients discontinued niacin ER due to adverse effects. [40]

(3) One hundred twenty-two patients enrolled in a 25 week trial of niacin ER (prescription product-Niaspan®, Kos Pharmaceuticals) 1-2gm/day at bedtime. Eleven percent of niacin ER patients discontinued for excessive flushing and 1.2% due to increased LFTs (< 3x ULN) (no significant difference versus placebo).[41]

C. Conclusion

1. **There have been numerous case reports of elevated LFTs[10] (Nature's Plus[42], Rugby Laboratories[43], Major Pharmaceuticals[44], Nicobid[â 44], Goldline[45], Endur-Acin[â 45], and Niatrol[45]) and fulminant hepatic failure leading to transplantation[48] or death[49] (United Research Laboratories) with niacin SR OTC products.**

2. **Since the introduction of niacin ER (prescription product- Niaspan[â], Kos Pharmaceuticals) in August of 1997, the adverse effect profile including elevated LFTs (approximately 1-2%) are consistent with the previously summarized trials.[50]**

3. **Niacin ER (prescription product- Niaspan[â], Kos Pharmaceuticals) is the product of choice due to its proven efficacy in dyslipidemia, favorable safety profile versus niacin SR, and improved patient tolerability versus niacin IR.**

4. **Niacin ER (prescription product- Niaspan[â], Kos Pharmaceuticals) may be used in patients that fail to reach their therapeutic goals or are unable to tolerate niacin IR. Niacin ER (prescription product- Niaspan[â], Kos Pharmaceuticals) is commercially available as the titration starter pack, 500 mg, 750 mg, and 1000mg tablets, all of which should be made available for use.**

Written by Rodney J. Gedey, PharmD. Pharmacy Practice Resident at University of Illinois at Chicago and Christine Chandler, PharmD. VHA Pharmacy Benefits Management

COST FOR HYPERLIPIDEMIC DRUG THERAPY

DRUG	USUAL DOSE [a]	VHA COST/MONTH [b]
Bile Acid Resins		
Cholestyramine Powder	4 gm bid	$ 23.50
Colestipol Granules [c]	5 gm bid	$ 18.60
Colestipol Tablets [c]	4 gm bid	$ 18.00
Fibrates		
Fenofibrate	201 mg qd	$ 36.88
Gemfibrozil [c]	600 mg bid	$ 4.00
HMG CoA Reductase Inhibitors		
Lovastatin [c]	10-80 mg qd	$12.00 - $ 60.60
Simvastatin [c]	5-80 mg qd	$13.50 - $ 32.10
Atorvastatin	10-40 mg qd	$ 34.74 - $ 64.80
Cerivastatin [d]	0.2-0.4 mg qd	$16.83 all doses
Fluvastatin [d]	20-40 mg qd	$ 21.71 all doses
Pravastatin	10-40mg qd	$ 30.97 - $ 55.99
Niacin Immediate Release [c, e]		
Niacor [â]	500 mg tid	$10.79
Niacin Extended Release [c, e]		
Niaspan [â]	1.5 g (2 x 750 mg) qd	$ 20.53

[a] Usual doses; does not reflect equivalent doses

[b] VHA Federal Supply Schedule (FSS) prices as of 6/99; updated prices may be obtained from the Pharmacy Benefits Management Website at www.dppm.med.va.gov

[c] VHA National Formulary Item

[d.] All dose strengths are uniformly priced

[e.] Food and Drug Administration (FDA) approved niacin product

[1] Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. J Am Coll Cardiol 1986;8:1245-1255.

[2] United States Pharmacopeial Convention. United States Pharmacopeia: The National Formulary. Rockville: United States Pharmacopeial Convention, Inc; 1995.

[3] McKenney JM, Proctor JD, Harris S, et al. A comparison of the efficacy and toxic effects of sustained vs immediate release in hypercholesterolemic patients. JAMA 1994;271:672-677.

[4] Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action. Metabolism 1985;34:642-650.

[5] Jacobson TA, Chin MM, Fromell GJ, et al. Fluvastatin with and without niacin for hypercholesterolemia. Am J Cardiol 1994;74:149-154.

[6] Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. Arch Intern Med 1994;154:1586-1595.

[7] McKenny JM, McCormick LS, Weiss S, et al. A randomized trial of the effects of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia. Am J Med 1998;104: 137-143.

[8] Knopp RH, Alagona P, Davidson M, et al. Equivalent of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. Metabolism 1998;47:1097-1104.

[9] McEvoy GK, editor. American Hospital Formulary Service Drug Information. American Society of Health-System Pharmacists. Bethesda: 1999.

[10] Rader JI, Calvert RJ, Hathcock JN. Hepatic toxicity of unmodified and time-release preparations of niacin. Am J Med 1992;92: 77-81.

[11] Ferenchick G, Rovner D. Case report; hepatitis and hemataemesis complicating nicotinic acid use. Am J Med Sci 1989;298:191-193.

[12] Patterson DJ, Dew EW, Gyorkey F, et al. Niacin hepatitis. Southern Med J 1983;76:239-241.

[13] Rourk RM, Rehman NU. Niacin. Help for your cholesterol—harm for your liver. N C Med J;59:87-88.

[14] Patel SD, Taylor HC. Intrahepatic cholestasis during nicotinic acid therapy. Cleve Clin J Med 1994;61:70-75.

[15] Tato F, Vega GL, Grundy SM. Effects of crystalline nicotinic acid-induced hepatic dysfunction on serum low-density lipoprotein cholesterol and lecithin cholesterol acyl transferase. Am J Cardiol 1998;81:805-7.

[16] Clementz GL, Holmes AW. Nicotinic acid-induced fulminant hepatic failure. J Clin Gastroenterol 1987;9:582-584.

[17] Reimund E, Ramos A. Niacin-induced hepatitis and thrombocytopenia after 10 years of niacin use. J Clin Gastroenterol 1994;18:270-271.

[18] Rindone JP, Arriola OG. Experience with crystalline niacin as the preferred drug for dyslipidemia in a specialty clinic. Pharmacotherapy 1997;17:1296-1299.

[19] Gardner SF, Schneider EF, Granberry MC, et al. Combination therapy with low-dose lovastatin and niacin is effective as higher-dose lovastatin. Pharmacotherapy 1996;16:419-423.

[20] Gardner SF, Marx MA, White LM, et al. Combination of low-dose niacin and pravastatin improves the lipid profile in diabetic patients without compromising glycemic control. Ann Pharmacother 1997;31:677-682.

[21] Henkin Y, Oberman A, Hurst DC, et al. Niacin revisited: clinical observations on an important but underutilized

drug. Am J Med 1991;91:239-246.

[22] Gibbons LW, Gonzalez V, Gordon N, et al. The prevalence of side effects with regular and sustained-release nicotinic acid. Am J Med 1995;99:378-384.

[23] Garg A, Grundy SM. Nicotinic Acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. JAMA 1990;264:723-6.

[24] Mostaza JM, Schulz I, Vega GL, et al. Comparison of pravastatin with crystalline nicotinic acid monotherapy in treatment of combined hyperlipidemia. Am J Cardiol 1997;79: 1209-1301.

[25] Lal SM, Hewett JE, Petroski GF, et al. Effects of nicotinic acid and lovastatin in renal transplant patients: a prospective, randomized, open-labeled crossover trial. Am J Kidney Dis 1995;25:616-622.

[26] King JM, Crouse JR, Terry JG, et al. Evaluation of effects of unmodified niacin on fasting and postprandial plasma lipids in normolipidemic men with hypoalphalipoproteinemia. Am J Med 1994;97:323-331.

[27] Vega GL, Grundy. Lipoprotein responses to treatment with lovastatin, gemfibrozil, and nicotinic acid in normolipidemic patients with hypoalphalipoproteinemia. Arch Intern Med 1994;154:73-82.

[28] Personal Communication, Sue Crane, Rugby Laboratories, 2725 Northwoods Parkway, Norcross, GA 30071, 1-800-645-2158, May 1999.

[29] Personal Communication, Olivine Young, 1900 West Commercial Blvd, Ft Lauderdale, FL 33309, 1-800-327-4114 extension. 4181, June 1999.

[30] Personal Communication, Michael Pfeiffer, Upsher-Smith Laboratories, Inc., 14905 23rd Avenue North, Minneapolis, MN 55447, 1-800-654-2299, June 1999.

[31] Davignon J, Roederer G, Montigny, et al. Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. Am J Cardiol 1994;73:339-345.

[32] Sposito AC, Caramelli B, Serrano CV, et al. Effect of niacin and etofibrate association on subjects with coronary artery disease and serum high-density lipoprotein cholesterol < 35mg/dl. Am J Cardiol 1999;83:98-100.

[33] Gray DR, Morgan T, Chretien SD, et al. Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. Ann Intern Med 1994;121:252-258.

[34] Keenan JM, Wenz JB, Rispin CM, et al. A clinical trial of oat bran and niacin in the treatment of hypelipidemia. J Fam Pract 1992;34:313-319.

[35] Aronov DM, Keenan JM, Akhmedzhanov NM, et al Clinical trial of wax-matrix sustained release niacin in a Russian population with hypercholesterolemia. Arch Fam Med 1996;5:567-575.

[36] Keenan JM, Chul-Young B, Fontaine PL, et al. Treatment of hypercholesterolemia: comparison of younger versus older patients using wax-matrix sustained-release niacin. J Am Geriatr Soc 1991;40:12-18.

[37] Keenan JM, Fontaine PL, Wenz JB, et al. Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991;151:1424-1432.

[38] Vacek JL, Dittmeier G, Chiarelli T, et al. Comparison of lovastatin (20 mg) and nicotinic acid (1.2g) with either diet alone for type II hyperlipoproteinemia. Am J Cardiol 1995;76:182-4.

[39] Kos Pharmaceuticals. Niaspan Package Insert, 1997.

[40] Guyton, JR, Goldberg AC, Kreisberg RA, et al. Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. Am J Cardiol 1998;82:737-743.

[41] Morgan MM, Capuzzi DM, Guyton JR. A new extended-release niacin (Niaspan): efficacy, tolerability, and safety in hypercholesterolemic patients. Am J Cardiol 1998;82:29U-34U.

[42] Frost PH. All niacin is not the same [letter]. Ann Intern Med 1991;114:1065.

[43] Dalton TA, Berry RS. Hepatoxicity associated with sustained-release niacin. Am J Med 1992;93:102-4

[44] Henkin Y, Johnson KC, Segrest JP. Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. JAMA 1990;264:241-3.

[45] Etchason JA, Miller TD, Squires RW, et al. Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. Mayo Clin Proc 1991; 66:23-8.

[46] Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin [letter] JAMA 1990;264:181.

[47] Knopp RH. Niacin and hepatic failure [letter] . Ann Intern Med 1989;111:769.

[48] Mullin GE, Greenson JK, Mitchell MC. Fulminant hepatic failure after ingestion of sustained-release nicotinic acid. Ann Intern Med 1989;111:253-5.

[49] Fischer DJ, Knight LL, Vestal RE. Fulminant hepatic failure following low-dose sustained-release niacin therapy in hospital. West J Med 1991;155:410-412.

[50] Personal Communication, Bruce Schrader, Kos Pharmaceuticals, Inc., 101 Brickell Drive, 25th Floor, Miami FL 33131, May 1999.