Abstract: Mipomersen is an antisense oligonucleotide inhibitor of apolipoprotein (apo) B-100 currently in phase 3 of development for the treatment of hyperlipidemia in patients with a high risk for cardiovascular disease. The drug acts by inhibiting the production of apoB-100, which is the structural core for all atherogenic lipids, including low-density lipoprotein cholesterol (LDL-C). The agent has been shown to produce significant reductions in LDL-C from baseline values compared with placebos. Clinical trials have demonstrated that mipomersen reduces LDL-C up to 44% in patients with familial hypercholesterolemia and patients with significantly elevated LDL despite taking maximum doses of statins. Unlike other medications that target apoB-100, such as microsomal triglyceride transfer proteins, mipomersen does not cause hepatic steatosis or intestinal steatosis and does not affect dietary fat absorption. Adverse side effects encountered with mipomersen include flu-like symptoms, injection site reactions, and elevated liver transaminases. If future studies continue to show such promising results, mipomersen would likely be a viable additional lipid-lowering therapy for patients who are at high cardiovascular risk, intolerant to statins, and/or not at target lipid levels despite maximum doses of statin therapy. Clinical outcome studies looking at cardiovascular disease end points still need to be done.

Key Words: mipomersen, antisense oligonucleotide, hyperlipidemia, familial hypercholesterolemia

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Coronary artery disease (CAD) is the leading cause of death in the United States and cardiovascular disease (CVD) accounts for one third of all deaths in the United States (33.6%), which is more than 2200 deaths per day, nearly 50% of which are directly related to CAD. The high incidence of CVD deaths is related to the high prevalence of associated risk factors, of which hypercholesterolemia is a major contributor. Approximately 33.6 million adults 20 years of age and older have a cholesterol level ≥240 mg/dL, which is a prevalence of 15% in the United States. Advances in treatment and improved patient education have reduced CVD mortality but the burden remains high. Cardiovascular surgical and invasive procedures have increased 27% between 1997 and 2007; the prevalence of CVD continues to increase and healthcare costs related to CVD continue to climb. The total cost related to CVD and stroke in the United States was estimated to be $286 billion in 2007, more than any other diagnostic group. The search for preventative treatment options is ongoing and robust. Not all available cholesterol-lowering drugs are tolerated by patients and some patients do not get an ideal clinical response from treatment. Most recently, interest in targeting apolipoprotein B-100 (apoB-100) as a new approach to reduce lipids has stimulated research programs. One such therapeutic agent is mipomersen, an antisense oligonucleotide (ASO) inhibitor of apoB-100, currently in phase 3 of clinical development. This article reviews the pharmacology and clinical use of mipomersen and discusses the potential role of this agent in medical practice.

APOB-100 AND ITS ROLE IN CVD

Low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for CAD and has been proven to be causally linked to the generation of atherosclerosis. LDL-C levels correlate in a linear relationship with relative risk of coronary heart disease (CHD) and, effective lowering of LDL-C has proven to reduce the risk of CHD. In light of these findings, the core of CVD treatment focuses on lowering LDL-C levels. Statin-based therapy has been the mainstay of treatment and has been shown to cause significant reduction in mortality from CVD. Unfortunately, this standard of care is still insufficient for many high-risk patients. Current guidelines for high-risk patients recommend LDL-C levels <70 mg/dL and a substantial number of patients are unable to achieve this goal with monotherapy. In fact, overall reduction in cardiovascular events has only been 30% despite LDL-C reduction up to 40%. As a result of these studies, significant medical need persists. The search for new targets of therapy has been widespread and data indicating apoB-100 as a risk factor for CAD have marked the lipoprotein as a center of research.

ApoB, the structural protein core of LDL-C (Fig. 1), has been shown to affect the transport, receptor binding, and removal of all atherogenic lipids. In the liver, the apoB gene is translated into apoB-100 and becomes the integral protein of very LDL. In the intestine, the apoB protein is integral in the formation of atherogenic lipids, its levels have been studied and correlated to cardiovascular risk. Elevated levels of apoB and LDL-C are associated with increased risk of atherosclerosis and CAD. ApoB elevations indicate abundant atherogenic lipid levels and therefore elevated CVD risk. The Apolipoprotein-related Mortality Risk Study indicated that elevated apoB is a more significant predictor of fatal myocardial infarction than LDL alone, and adds power to LDL in prediction of fatal myocardial infarction. On the other hand, genetic abnormalities that prevent the synthesis of apoB result in lower circulating LDL and are associated with reduced levels of atherosclerosis. This rare genetic abnormality, called familial hypobetalipoproteinemia (FHBL), results in apoB and LDL levels that are 25% to 50% of normal in heterozygotes and undetectable in patients who are homozygous for the mutation. In studying this patient population, strikingly low cardiovascular risk has been observed. As a result of these observations, research targeting inhibition of apoB synthesis is being explored.

MIPOMERSEN

Initial studies observed lipoprotein secretion after inhibition of the MTP. Unfortunately, blocking MTP with small molecular
inhibitors and MTP knockout mice led to hepatic steatosis, steatosis, and severely elevated levels of liver transaminases.14,15 Antisense DNA technology has been used in research to selectively reduce levels of a target messenger RNA (mRNA).16 Animal models that have used antisense DNA technology to target and reduce apoB mRNA showed reduction in circulating apoB protein levels and also a reduction in circulating LDL-C.17–19 Mipomersen, developed by ISIS pharmaceuticals, is an innovative drug that uses antisense technology to target and reduce apoB mRNA. This agent has been designed as a novel therapy to treat high-risk hypercholesterolemic patients.

**Mechanism of Action**

Mipomersen is a 20-mer ASO that is complementary to the coding region for human apoB mRNA and is administered by once weekly subcutaneous injection.17,20–22 ASOs are chemically modified single-stranded DNA molecules that have been proven safe and effective at reducing a specific mRNA of interest.16 These synthetic nucleic acid sequences are generally short (13–25 bases long), in the antisense orientation to the target mRNA and, when introduced to the organism, lead to gene silencing.16,23 The hybridization of the ASO to the mRNA of interest activates RNase H cleavage of the message, preventing protein translation and gene expression16,23 (Fig. 2). RNase H is a nonspecific endonuclease that hydrolyzes phosphodiester bonds of RNA when hybridized to DNA. As an ASO, mipomersen acts in the same manner, hybridizing endogenous hepatocyte mRNA, activating RNase H, and inhibiting protein translation. The complement of mipomersen’s oligonucleotide sequence is apoB-100 mRNA, which, as discussed earlier, becomes the principle structural protein of atherogenic lipoproteins. This mechanism for reducing LDL is unique; there have been no other drug trials attempting to inhibit apoB synthesis directly. Antisense-induced cleavage of mRNA creates a deficiency in apoB, analogous to FHBL, function, like in familial hypercholesterolemia, the response to statin therapy is inadequate even at maximum doses.23,24 As will be discussed in the following sections, studies examining the efficacy of mipomersen in this patient population have shown promising results when used as monotherapy and when added to standard statin therapy.21,22

**Pharmacokinetics**

ASOs have been studied for years and their uses have been evaluated in immunologic disorders and as cancer therapies.16,23,27–29 With extensive study, antisense therapy has undergone modification over the years. As single-stranded unmodified DNA molecules, first-generation ASOs are readily degraded by endonucleases and exonucleases, which are ubiquitous.16,23,27–29 The by-products of degradation of first-generation ASOs have been demonstrated to be toxic to cell growth and proliferation of healthy tissue.27,28 In the interest of improving the pharmacodynamic, pharmacokinetic, and toxic profile of ASO technology, a 2′-O-methoxymethyl modification has been developed by ISIS pharmaceuticals (Fig. 3).16,29 The 2′-O-methoxymethyl-modified oligonucleotides have consistently demonstrated superior resistance to nuclease degradation and demonstrate several orders of magnitude greater affinity for target mRNA.29 ASOs modified in such a fashion have been called second-generation ASOs.30 Extensive study in animals has demonstrated that second-generation ASOs are safe and effective, and drug levels correlate with pharmacologic activity.30,31 Mipomersen is one of these second-generation ASOs.

The pharmacokinetic properties of mipomersen were studied in mouse models, monkey models, and in humans.20,31 The first human study examining the pharmacokinetics and dynamics of mipomersen showed it has a similar profile to that of animal models; therefore, comparisons can be made across species.31 After parenteral administration, plasma concentration profiles demonstrated a rapid distribution phase followed by a slow elimination phase and indicated that exposure was predictable on an milligram per kilogram basis.31 Absorption was nearly complete following subcutaneous injection with bioavailability ranging from 80% to 100%.31 Studies in humans showed dose-dependent maximum plasma concentrations ranging from 4.8 to 21.5 μg/mL (50–200 mg dosing) at the end of a 2-hour intravenous (IV) infusion and a maximum plasma concentration of 1.0 to 2.7 μg/mL after subcutaneous dosing.20 Despite the differences in peak concentrations, IV and subcutaneous dosing showed similar
plasma area under the curve drug concentrations. Elimination data indicated that the majority of mipomersen was removed from plasma by distribution to tissues within the first 24 hours after drug administration. The plasma half-life was short, measured in minutes, whereas tissue half-life was prolonged, measured in days. In humans, tissue half-life ranged from 23 days in the 50-mg dosing group to 31 days in the 200-mg dosing group. The slow elimination time allows for maintenance of tissue concentrations and effective pharmacologic activity despite infrequent dosing. Consistent with the prolonged half-life, steady state is estimated to be reached at 26 weeks. Although whole body distribution was the mechanism of plasma clearance, it was found that tissue clearance was dependent on endonuclease and exonuclease degradation of the ASO and, to a lesser extent, elimination through urine and stool. As a second-generation ASO, mipomersen is more resistant to degradation by endo/exonucleases contributing to the prolonged tissue half-life. It appears that mipomersen is highly bound to plasma proteins as renal elimination was minimal until enormous doses were given to saturate plasma protein-binding sites. Furthermore, pharmacokinetic studies did not show interaction with either simvastatin or ezetimibe elimination nor distribution.

Clinical Trials

The primary indications for which mipomersen has been studied include hypercholesterolemia in patients at high cardiovascular risk, hypercholesterolemia in patients on stable statin therapy, and patients with homozygous familial hypercholesterolemia. Currently in an open-label phase 3 trial, mipomersen has been studied in multiple open-label, phase 3 clinical trials. These trials will be discussed in the ensuing section and the results are summarized in Table 1.

The first human study was a randomized, double-blind, placebo-controlled, dose-escalating trial designed to establish efficacy and tolerability of mipomersen in healthy patients with normal LDL levels. Subjects were healthy volunteers 30 to 64 years of age with fasting cholesterol levels <300 mg/dL. Study end points included safety and tolerability, pharmacokinetics of study drug, and efficacy. Mipomersen was administered by 1 subcutaneous dose of 50, 100, 200, or 400 mg/week followed by a 4-week observation period. After the 4-week observation period, subjects entered a multiple-dose phase where the same dose was administered by 3 alternate day IV infusions. The multiple-dose phase was designed to reach 70% hepatic tissue steady state in the first week. After the alternate day IV dosing, subjects were then administered the study drug by 3 weekly subcutaneous injections. Subjects were followed for up to 12 weeks or until cholesterol returned to ≥90% of baseline. Administration of mipomersen revealed a dose-dependent prolonged reduction in apoB-100. The 200-mg dose group reduced apoB levels up to 50% within 72 hours of the last dose. A prolonged and dose-dependent reduction in LDL-C was also observed with the maximum percentage reduction of 35% in the 200-mg dose group. ApoB and LDL-C remained below baseline for 90 days in the majority of 200-mg treatment subjects.

Total cholesterol showed a maximum reduction of 27% and 40% in the 200- and 400-mg study groups, respectively. The drug was well tolerated and no patients reported serious adverse reactions.

Mipomersen has also been studied in comparison with standard statin therapy. This phase 2 study compared mipomersen to placebo in hypercholesterolemic patients (LDL-C levels between 100 and 220) on stable statin therapy. Seventy-four patients between

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**FIGURE 2.** Antisense oligonucleotide (ASO) mechanism of action. Mipomersen is an ASO inhibitor of apolipoprotein B-100 messenger RNA (mRNA). An ASO is a single-stranded DNA molecule (light gray) that hybridizes to an mRNA of interest (dark gray). When hybridized into a duplex, RNase H is activated, which then cleaves the phosphodiester bonds of the mRNA. The ASO is resistant to RNase H degradation and is recycled to target additional mRNA.

**FIGURE 3.** Mipomersen oligonucleotide sequence and 2’-MOE modification. Data from Dias and Stein, Crooke, and Yu et al.
the ages of 49 and 65 years were randomly assigned by dose cohort to either placebo or mipomersen. Cohorts were further divided into 5-week dose-escalating cohorts or to a 200 mg/week 13-week cohort. Mipomersen produced significant incremental lipid-lowering effects compared with placebo in patients receiving stable statin therapy. The outcomes of this study observed an increased proportion of patients who reached target LDL-C levels after completion of the study. Mipomersen was shown to reduce apoB and LDL in a dose-dependent fashion from the on-statin baseline. In the 13-week cohort receiving 200 mg/week, an average incremental reduction in apoB and LDL-C of 36% was observed from baseline 2 weeks after the last dose. Reductions in LDL-C and apoB were greater in the 13-week cohort compared with the 5-week cohort at the same dose. LDL-C levels decreased up to 49% in comparison to the placebo cohort at mipomersen doses ≥100 mg. These results are comparable to studies evaluating lipid-lowering effects of statin adjunct therapies.

Current lipid-lowering therapies rely on upregulation of LDL receptors to reduce circulating LDL. In patients with nonfunctional LDL receptors, such as patients with familial hypercholesterolemia, statin therapy has resulted in insufficient reductions of LDL. The most recently published prospective study of mipomersen has been completed in a study population of familial hypercholesterolemia, where 51 patients with a mean age of 31.3 years who have a diagnosis of homozygous familial hypercholesterolemia, either by genetic testing or by clinical evaluation (LDL >13 mmol/L with xanthomas before age 10 years or parents with heterozygous familial hypercholesterolemia), were randomized 2:1 to receive 200 mg mipomersen or placebo. The study drug was administered by weekly subcutaneous dosing for 26 weeks. The study observed an average reduction of 25% in LDL-C (3% reduction in placebo group) despite 88% of subjects being treated with maximum doses of statins. Although the majority of patients showed reductions in LDL-C ≥18%, there was wide variability in LDL-C lowering effect, ranging from 2% to 82%. The study did not show correlation between receptor mutation type and response to study drug. Moreover, reductions in lipoprotein(a) [Lp(a)] were also observed. Briefly, Lp(a) is an LDL-like lipoprotein that consists of an apoB protein covalently linked to apo(a). In studies adjusted for sex and age, Lp(a) showed an association with the risk of CHD in a log-linear fashion and there is sufficient evidence to support Lp(a) as a causative agent in generation of atherosclerosis. Reductions in Lp(a) have not been found in patients treated with statins. Additional studies evaluating Lp(a) reductions in mipomersen-treated mice found that mipomersen reduced Lp(a) levels up to 60%. Other findings of this phase 3 clinical trial included elevations in high-density lipoprotein cholesterol (HDL-C), no significant change in apo(a) levels, and an average reduction in HDL-C/LDL-C ratio of 34%. Data indicated that on average, maximum effect of the study drug took 17 weeks.

Most recently, Genzyme and ISIS Pharmaceuticals presented the results of ongoing phase 3 clinical trials at the American College of Cardiology’s 60th annual Scientific Session. The presentation included 2 phase 3 clinical trials. The first abstract presented a double-blind, randomized 2:1 (treatment: placebo) trial of 58 patients with severe familial hypercholesterolemia (severe is defined as LDL-C ≥300 mg/dL or ≥200 mg/dL with CHD) to receive weekly subcutaneous dosing of 200 mg mipomersen or placebo. Over the 26-week treatment period, a reduction in LDL-C by 36% was observed in the mipomersen group, corresponding with an average reduction of 101 mg/dL, compared with a 13% LDL-C increase in the placebo group. Mipomersen-treated patients also exhibited a 36% reduction in apoB (11% increase in placebo), a 33% decrease in Lp(a) (1% reduction in placebo), and a 34% reduction in non-HDL-C (14% increase in placebo). There was no significant change in HDL-C with mipomersen. The lipid-lowering effects of mipomersen in this patient population have been shown after failed courses of standard lipid-lowering therapy. These data present promising results for a patient population that is resistant to current standards of care. The second abstract presentation was that of a phase 3 clinical trial of patients with hypercholesterolemia (LDL-C

### TABLE 1. Summary of Hyperlipidemia Trials Conducted with Mipomersen

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Demographics</th>
<th>Trial Design, Duration</th>
<th>Treatment (mg/dL)</th>
<th>Baseline Lipids (mg/dL)</th>
<th>Mean Lipid Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastelein et al20</td>
<td>n = 36 healthy volunteers, 30–64 years old</td>
<td>R, DB, PC, DE 12 wk</td>
<td>50, 10, 200, 400</td>
<td>TC: 219 ± 27 LDL-C: 128 ± 22</td>
<td>LDL-C: 35% (200 mg) TC: 27% (200 mg)</td>
</tr>
<tr>
<td>Akdim et al21</td>
<td>n = 74 volunteers, 49–65 years old on stable statin therapy for at least 3 mo</td>
<td>R, DB, PC, DE 6 cohorts: 5–5 wk; 1–13 wk</td>
<td>5 wk cohort: 30, 100, 200, 300, 400 13 wk: cohort: 200</td>
<td>5 wk (n = 62); LDL-C 135 13 wk (n = 12): LDL-C 127</td>
<td>73% of 200 mg group reach LDL-C &lt;100; 51.8% ± 14.3% (300 mg) 13 wk: 35.8% ± 16.4% (200 mg)</td>
</tr>
<tr>
<td>Raal et al22</td>
<td>n = 51 FH patients, mean age 31.3 yr on stable lipid lowering</td>
<td>R 2:1, DB, PC 26 wk</td>
<td>200</td>
<td>TC 502 LDL-C 440 Lp(a) 23.2</td>
<td>LDL-C: 24.7% ± 3% Lp(a): 31.3% ± 8%</td>
</tr>
<tr>
<td>Genzyme Corp38</td>
<td>n = 58 severe FH patients on maximum doses of lipid lowering</td>
<td>R 2:1, DB, PC 26 wk</td>
<td>200</td>
<td>LDL-C 276</td>
<td>LDL-C: 36% Apo-B: 36% Lp(a): 33%</td>
</tr>
<tr>
<td>Genzyme Corp38</td>
<td>n = 158 hypercholesterolemia patients (LDL-C &gt;100) at high risk of CHF taking maximum doses of statins</td>
<td>R 2:1, DB, PC 26 wk</td>
<td>200</td>
<td>LDL-C 123</td>
<td>LDL-C: 37%; 50% of mipomersen-treated groups reached LDL-C &lt;70 mg/dL</td>
</tr>
</tbody>
</table>

R indicates randomized; DB, double blind; PC, placebo controlled; DE, dose escalating; TC, total cholesterol; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FH, familial hypercholesterolemia; CHF, congestive heart failure.
>100 mg/dL) who were at high risk of developing CHD while taking maximally tolerated doses of statins. This randomized, double-blind, placebo-controlled trial (2:1 treatment:placebo) observed 158 patients over a 26-week treatment course of once weekly 200 mg subcutaneous mipomersen. At the end of the treatment course, patients had an average LDL-C level of 75 mg/dL, representing an average reduction of 37% from baseline. In fact, half of the mipomersen-treated patients who were not at goal despite statin therapy achieved LDL-C levels <70 mg/dL, the recognized treatment goal for high-risk patients. These patients also demonstrated significant reductions in apoB, Lp(a) and non-HDL-cholesterol. There was no significant reduction in HDL-C from baseline with mipomersen. Similar to previous studies in familial hypercholesterolemia patients, the cholesterol-lowering benefit of mipomersen was observed, in addition to those achieved with patients’ concurrent statin regimens. Again, all data available on mipomersen-treated cohorts indicate that mipomersen is an effective lipid-lowering therapy for high-risk patients who are not at goal despite maximally tolerated doses of standard lipid-lowering therapy. Overall, the benefit of mipomersen on cardiovascular outcomes still needs to be determined, comparing the drug to statins and other lipid-lowering therapies.

**Adverse Effects**

In general, mipomersen is safe and very well tolerated. Common adverse effects reported in clinical trials include injection site reaction, flu-like symptoms, and liver transaminase increases. No patient in clinical trials showed adverse effects in renal function, muscle, platelet count, or blood pressure, and no patient developed antibodies to mipomersen. Inhibition in apoB-100 synthesis also did not exhibit the gastrointestinal side effects, intestinal steatosis, or malabsorption that MTP inhibition had shown.14,15 Injection site reactions were the most common adverse effects occurring in up to 76% of patients according to a phase 3 trial21; this finding was similar to previous studies (72%)24 and is consistent with recent ongoing clinical trials.35 Injection site reactions occurred 3 times more often in the treatment group than placebo. Most of these reactions were described as mild, erythematous, painless, and resolved after 24 hours. Other reports of injection site reactions include hematomas, pain, pruritis, discoloration, and swelling. These injection site reactions were mild and resolved within days of treatment, but many did recur with follow-up dosing. Injection site reactions also occurred in trials studying different potential ASOs.18 To date no evidence of autoimmunity has been observed, though long-term monitoring of this potential adverse reaction must be followed up with care.

Flu-like symptoms were the second most common complaint.38 The symptoms occurred shortly after administration of mipomersen, resolved within days, and were observed to occur with greatest frequency in the first few doses. That being said, the number of events was similar to the placebo group.

Transaminase elevations (ALT) were the most concerning adverse effects discovered in the study of mipomersen. Hepatic function has been studied carefully because hepatic steatosis has been observed in previous studies targeting apoB.14,15 As discussed previously, apoB is obligatory in the processing and secretion of triglycerides from the liver; inhibition of triglyceride secretion may lead to buildup within hepatocytes. In fact, many patients with FHBL, the model for mipomersen, developed hepatic steatosis.15 However, preclinical animal studies of mipomersen failed to show hepatic fat accumulation resulting from apoB-100 synthesis inhibition.14,16 In clinical studies, 50% of mipomersen-treated subjects exhibited elevations in ALT >1 × the upper limit of normal (ULN) but <3 × ULN. This was similar to proportion of events in the placebo group. Ten to 15% of patients in phase 2 and phase 3 trials21,22,38 exhibited increases in ALT >3 × ULN versus no occurrences in the placebo group. Subjects with ALT elevations >3 × ULN did not show concomitant increase in bilirubin or prothrombin time and were all asymptomatic. Mipomersen administration was terminated in these subjects and ALT levels returned to normal within 2 weeks. Four of these patients with elevated liver transaminase levels were evaluated for hepatic fat accumulation by magnetic resonance imaging. Only one of these patients exhibited elevations in hepatic fat from baseline (9.6%–24.8%). As indicated in the study, this patient had a particularly robust response to mipomersen with LDL-C reduction of 75% from baseline.33 Unfortunately, baseline hepatic fat was not available for all subjects and only subjects with ALT elevations were evaluated by magnetic resonance imaging. To further assess mipomersen and the potential for hepatic triglyceride buildup, a randomized, double-blind, placebo-controlled study of 21 patients with familial hypercholesterolemia was completed.39 As described in the clinical studies earlier, these subjects who were already receiving stable lipid-lowering therapy were randomized to receive weekly subcutaneous 200 mg mipomersen or placebo. Proton magnetic resonance spectroscopy was used to evaluate intrahepatic triglyceride content. Only 1 subject in the mipomersen treatment group (10%) developed mild hepatic steatosis, which was transient and resolved after termination of the study drug. No patient treated was observed to develop significant hepatic steatosis. That being said, this study was a small sample size evaluated over a short time period. Mipomersen has been found to reach steady state after 26 weeks, whereas this study observed patients for only 15 weeks. More long-term studies evaluating hepatic fat accumulation must be completed before a determination of hepatic steatosis risk can be made. Ongoing, phase 3 clinical trials presented at the 60th annual American College of Cardiology’s presentation observed elevations in ALT similar in character to previous studies.37 Ten to 15% of mipomersen-treated patients had persistent ALT elevations 3 × ULN during treatment period between the 2 presented studies. None of the patients had changes in laboratory tests indicating clinically significant hepatic dysfunction. Finally, ALT levels appeared to be associated with rapid and significant reductions in LDL-C.

**Dosing**

The most common dose of mipomersen used in hypercholesterolemia is 200 mg/week given subcutaneously. This dose effectively reduces LDL-C and Lp(a) and is comparable with other standard lipid-lowering therapies, shows similar efficacy to other statin adjunctive therapies, and is well tolerated. Administering <100 mg/week has not shown lipid-lowering results effective enough to reach therapeutic levels in high-risk patients. No drug interactions have been observed to date. Mipomersen is metabolized by endogenous endonucleases and exonucleases and as such, dosing does not need to be adjusted in patients with renal insufficiency. To date, studies evaluating hepatic fat accumulation have excluded patients who are at high risk of developing fatty liver. Mipomersen should be used with caution in patients who are at high risk of developing hepatic steatosis until long-term studies have been completed.

**CONCLUSIONS**

Mipomersen is a unique lipid-lowering drug that uses antisense technology to precisely and effectively reduce apoB-100 and LDL-C with an additional benefit of reducing Lp(a).37-40 Clinical trials in hypercholesterolemia have shown the drug to be highly effective and safe as a lipid-lowering agent when used as monotherapy or in conjunction with stable statin therapy. In addition, the drug has shown to increase HDL levels and reduce Lp(a) levels providing additional cardiovascular protection. To date, there is limited experience with the use of mipomersen in patients using lipid-lowering therapy other than statins, and long-term cardiovascular outcomes studies with this therapy need to be carried out.
REFERENCES


