ORIGINAL CONTRIBUTION

Attitudes and Expectations of Graduating Canadian Medical Students Toward Their Future

Step 1: Dalhousie University Medical School

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With the ongoing climate changes in Canadian medical practice, there is some concern that this country will be unable to provide the potential lifestyles that its future physicians will demand. This study aims to take the first step in the process of gathering information on the attitudes and expectations of graduating Canadian medical students for the purposes of developing a basis against which to compare predictions for the future. Dalhousie University was used as the starting point for this study and numerous insights were gained into the factors that influence the decisions made by the students at that school. The next logical step is to apply the survey to graduating classes at all Canadian medical schools. It is hoped that the knowledge gained from this survey about the expectations of Canadian medical students can be compared both to current working conditions for practicing physicians and to predicted future practice patterns. Addressing discrepancies between expectations and realities will improve retention and career satisfaction among Canadian physicians.

INTRODUCTION

In Canada today, the climate of medical practice is continually changing. This is occurring for a number of reasons, but societal, technological, economic, political, environmental, ethical, and educational factors all have a role to play[1]. Not least among these are the financial considerations that are so much in the minds of many of this country's medical students. Debt loads are continually increasing, while the earning power of physicians in this country is dropping[2]. These as well as many other external factors are combining to play a major role in the specialty choice of today's medical students.

While the practice environment for new Canadian physicians is changing, so too are the needs of the soon-to-be doctors in our country. There is a greater and greater influence of lifestyle considerations for these people. New medical graduates often have lifestyle expectations that differ greatly from those of their predecessors[3].

With the ongoing changes in Canadian medical practice such as these, there is some concern that, in the near future, this country may not be able to provide an environment that new physicians will deem acceptable. Expectations about the quality of life for a new physician may cause more and more Canadian doctors to migrate to other parts of the world (e.g. the U.S.), where the conditions may be more favorable. In fact, in recent years there has been a relative increase in the movement of physicians to the United States and more Canadian students have been applying to American medical schools[4]. Situations such as these have prompted the need for a serious look at the factors that may influence the future situation of Canadian medical practice.

One of the main purposes of this study was to begin the process of gathering data on current expectations and attitudes of Canadian medical students through the use of an email survey. The areas of interest included in the survey are: specialty choice, income, family / leisure time, control over schedule, responsibility, stress / pressure, job security, practice location, retirement age, debt load, and demographics. Once this process has been completed, it is intended that this information will be compared to predictions concerning the potential lifestyles that this country will be able to offer its new physicians. This is so that potential discrepancies between working conditions and expectations can be identified as soon as possible.

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As with all major undertakings, these first steps are as much a learning experience as a foundation for further progress. The medical school at Dalhousie University was chosen as the first place to gather data and to refine the data collecting techniques. This paper describes the steps taken in the administration of the questionnaire used to survey graduating medical students at this school, the results attained from this effort, and a discussion of how to continue with the study in light of these results. It is expected that the lessons learned here will be applied to efforts to survey the remaining English-speaking Canadian medical schools. A reliable reflection of the current attitudes and expectations of English-speaking Canadian medical students will be useful in determining potential steps to be taken to improve the state of medical practice in Canada.

METHODS

The main tool used for this study was an email questionnaire. The steps followed for the creation and administration of this questionnaire were, as reasonably as possible, those of the *Dillman Total Design Method*[1]. The main purpose for using this method was to attempt to maximize response rates, thus enabling a better representation of the attitudes and expectations of the general population of graduating Dalhousie medical students.

During the pilot study involving a small group of five potential respondents, it was found that the questionnaire took approximately six minutes to complete and, for the most part, the multiple choice options provided for each question were adequate. The questionnaire was also submitted to colleagues and potential users of the data for input on design and usefulness.

Minor changes were made to the questionnaire following the pilot study and then the final version of the questionnaire was emailed to all members of the fourth year class. The original mailing was followed by a series of reminders at one-week intervals. A similar method of follow-up has been shown to more than double response rates in most instances[5]. This study showed a return rate of approximately 19% after the original mailout. After the first follow-up, the response rate rose to just under 50%. The final follow-up consisted of a personal visit to the fourth-year class with a hard copy of the questionnaire. This resulted in a final response rate of 60%.

Once the surveys were received, the responses were input to a spreadsheet. Before statistical analysis was begun, the data were verified for correctness and the original email surveys were deleted as promised by the consent form that preceded the questionnaire in each mailout to the potential respondents.

This research was approved by the research ethics board of Dalhousie University.

RESULTS

Statistical Tests

For each potential response in the questionnaire, a number of statistical tests were performed in order to analyze the data. For each question, the modal response and the percentage of respondents choosing the modal response was calculated. In addition, for the questions with graded responses, the median, mean, and standard deviation were calculated. Due to length constraints, this data has not been included here but is available from the author upon request.

Response Rates

Although there were eighty-three students in the fourth year class at Dalhousie University during this study, not all were included in the sample. Five of the students were from Malaysia, and were therefore ineligible to do their postgraduate training in Canada. As a result, it was felt that including these students in the survey was not appropriate as they would not have an effect on the future situation of medical practice in Canada. As well, one non-Malaysian student responded to the mailout expressing regret in his inability to complete the questionnaire before the due date. He too was dropped from the sample, bringing the total number of potential respondents down to seventy-seven. Of those seventy-seven, forty-six questionnaires were completed and returned in time for the writing of this report. The unreturned questionnaires were classified as refusals. The response rate was therefore calculated as follows:

$$\text{Response Rate} = \frac{\#\ \text{Returned}}{\#\ \text{in sample} - (\text{noneligible} + \text{nonreachable})} \times 100$$

$$= \frac{46}{83 - (5 + 1)} \times 100 = 60\%$$

Demographics:

Of the forty-six respondents, twenty-four were males and twenty-two were females. Not all of the respondents completed every question in each questionnaire, so the denominator varied to a maximum of forty-six for calculations on individual questions. Of the respondents, 69% were between the ages of twenty-four and twenty-six, while an additional 24% were between the ages of twenty-seven and twenty-nine. All were expecting to graduate in 1999 and all were Canadian citizens. Eighteen percent were married while the remaining 82% were single at the time of the study. None of the respondents indicated that they had dependents, although 73% expected they would have at least one dependent while practicing medicine.

Career Choice:

The first question posed in the questionnaire sought the respondent's choice of career. Results showed that 54%

Table 1: Variables Relating to Career Choice

Category	Selected Responses	Choice of Career			Correlation
		Family Practice	Clinical Medicine	Surgery	
Age at Graduation	>26	29%	57%	14%	-0.29
	24-26	10%	52%	32%	
Debt at Graudation	none	0%	67%	33%	0.05
	$1 - $10,000	50%	25%	25%	
	$10,001 - $20,000	0%	0%	0%	
	$20,001 - $40,000	18%	64%	18%	
	$40,001 - $60,000	13%	63%	25%	
	$60,001 - $80, 000	17%	50%	33%	
	> $80,000	11%	56%	33%	
Marital Status	Single	11%	54%	30%	
	Married	38%	50%	13%	
Desired Responsibility	Moderate	15%	62%	23%	0.04
	Great deal	16%	55%	29%	
Desired Stress/ Pressure	Very Little	0%	100%	0%	0.04
	Moderate	18%	53%	29%	
	Great deal	0%	50%	50%	
	Undecided	0%	100%	0%	
Desired Income	$40,001 - $80,000	0%	100%	0%	0.41
	$80,001 - 160,000	25%	75%	0%	
	$160,001 - 250,000	18%	41%	41%	
	> $250,000	0%	20%	80%	
Desired Number of Hours per week worked	>20	0%	100%	0%	0.10
	21 - 40	33%	67%	0%	
	41 - 60	14%	59%	28%	
	61 - 80	25%	38%	38%	
	81 - 100	0%	0%	100%	
	> 100	0%	100%	0%	
Desired Control Over schedule	Moderate	25%	50%	25%	0.09
	Great Deal	5%	62%	33%	

were destined for a clinical medical specialty, 26% for surgerical specialties, 15% for family practice, and 4% for a laboratory specialty. In an attempt to find links between career choice and certain other aspects of the respondents, comparisons were made to a number of variables, including age, debt load, marital status, number of dependents, and desired levels of family / leisure time, responsibility, stress / pressure, income, and control over schedule. This career choice data is compiled in *Table 1*. Please note that the percentage values shown correspond to their particular row.

Working Location:

Desired location of practice and desired living location were compared with the size of the respondent's home community. The degree of correlation between these categories was evaluated using correlation coefficients. These results are presented in *Table 2*.

For the purposes of this study, a correlation was not considered strong unless the corresponding correlation coefficient was greater than 0.6. Those that fell in the range of 0.3 to 0.6 were considered moderate, and anything less that 0.3 was considered to be indicative only of a weak correlation. None of the correlation coefficients calculated in this study indicated a strong correlation and a number of correlation coefficients proved to be negative, indicating that as the values in one category rose, those of another fell. Again, these negative correlations could be classified as strong, moderate, or weak.

Gender Variations:

Many responses were also compared on the basis of gender. For instance, of the 54% of respondents headed for a clinical medical specialty, 68% were females. Of the clinical medical specialties, internal medicine was the most popular choice, picked by 23% of females and by 17% of males who chose a clinical medical specialty. Anesthesia and psychiatry were the next most popular choices, with each claiming 20%. Of the surgical specialties, general surgery

Table 2: Variables Relating to Desired Location

		Desired Working Town Size				Desired Proximity to a Metropolitan Centre (km)					
		< 10k	10 - 50k	50 - 200k	> 200k	Metro Area	< 50	< 100	< 200	no pref	> 200
Home Town Pop.	< 10k	13%	25%	0%	25%	13%	13%	25%	25%	13%	0%
	10k - 50k	0%	11%	56%	22%	22%	22%	0%	22%	22%	0%
	50k - 200k	0%	0%	54%	23%	15%	15%	8%	38%	15%	0%
	> 200k	0%	13%	33%	40%	20%	27%	27%	20%	7%	0%
Correlation Coefficient:		0.07				-0.13					

DISCUSSION

and orthopedic surgery were the two most popular choices, achieving 33% and 25% of the popular choice, respectively. Three quarters of those who picked surgery were males.

Factors Influencing Career Practice Decisions:

Finally, the respondents were also asked to rank the top five factors influencing their career practice decisions. This data was compiled and the five most frequent responses are presented below in *Table 3*.

A tremendous amount of data was collected based on the survey results. Following the lead set in the *Results* section, only the most remarkable and / or pertinent results will be discussed here.

Response Rate:

Unfortunately, the response rate for this survey, at 60%, was lower than originally hoped. It is claimed that the Dillman Total Design Method will consistently produce response rates of 75 – 80% if used properly\f\h [5]. Many other surveys using this method have given even better rates[1]. Probably one of the biggest reasons for the lower response rate in this study was that the Total Design Method was not followed exactly, with perhaps the greatest discrepancy being in the method of follow-up. In this study, only two follow-ups were made after the original sample had been sent out, unlike the three follow-ups that Dillman suggests.

Another discrepancy and possible cause of the lower response rate was the fact that the questionnaire was sent using email. This may not have made much of a difference in many cases, but target population was not typical. Fourth year medical students receive many emails and, as a result, may only read those that they deem most relevant to their situations. As well, because of their busy schedules in the hospitals, they often do not spend much time at the school, where the email is normally accessed. Another possible factor is that some may have been on external rotations during the survey period and consequently unable to complete the questionnaire.

Finally, the time allowed for the return of the samples was only about three weeks from the original mailout. Dillman suggests that the third follow-up be sent on the seventh week. This allows more than two months for the receipt of completed questionnaires from the date of the first mailout. These factors may have combined to limit the response rate to the level observed.

In light of these limiting factors, a response rate of 60% should not be considered poor. In fact, if either of these factors had not been present, that is, if more time was available for the implementation of the questionnaire or the sample population was other than busy fourth year medical students, it is suspected that the response rate could have been significantly higher.

Responses for Individual Categories:

Thirteen main categories were surveyed in the questionnaire. These included: career choice, stress / pressure, responsibility, job security, income, debt load, family / leisure time, control over schedule, retirement age, practice location, specialty choice, ranking of influential factors, and demographics. The focus of this discussion will be the tables presented earlier in the *Results* section.

Career Choices:

A number of factors have been shown to influence a medical student's choice of career. Those analyzed here include age at graduation, debt load, marital status, desired responsibility, desired stress / pressure, desired income, desired

Table 3: Top Five Factors Influencing Career Practice Decisions

Factor	Frequency as One of the Top 5 Choices
1. Family/Leisure Time	15.2%
2. Type of Work	13.9%
3. Level of Responsibility	10.4%
4. Level of Stress/Pressure	10.0%
5. Level of Income	8.7%
6. Control over Schedule	8.7%

number of hours worked per week, and desired level of control over schedule. These results can be found in *Table 1*.

AGE AT GRADUATION AND MARITAL STATUS

It has been shown that, because of familial responsibilities, older graduates and married graduates are more likely to pursue family medicine[2]. This was seen in the data obtained in this study as well. Thirty-eight percent of the married respondents chose family practice, whereas the rate was only 11% for single respondents. As well, graduates older than twenty-six picked family practice 29% of the time and those aged 24 – 26 only picked this career path 10% of the time.

DESIRED FAMILY / LEISURE TIME AND RESPONSIBILITY

Both desired amounts of family / leisure time, measured in this study by desired number of hours worked per week, and desired level of responsibility have been shown to moderately influence career choice[3]. In fact, nearly 63% of respondents in this study said that lifestyle considerations were at least as influential as subject matter in their career choice. Also, this category was indirectly rated the third most influential factor on career choice by them. Few would disagree that the availability of family / leisure time is a major component of a controllable lifestyle. As well, desired level of responsibility occurred more often than any other factor in *Table 3*. Evidently, these variables have a considerable influence on career decision making.

DESIRED LEVEL OF STRESS / PRESSURE AND CONTROL OVER SCHEDULE

Both desired levels of stress / pressure and control over schedule have been shown to have a minor influence on career choice in at least one other study. However, it is interesting to note that respondents ranked these two variables fourth and fifth highest in their decisions (see *Table 3*). It would seem then that, at least to the respondents in this study, these factors play more of a role than the literature would otherwise lead us to believe.

INCOME

Desired level of income ranked number five in *Table 3*. In other studies, though, it has only proven to influence career choice in a minor way. However, when coupled with an increasing debt load, the reason for such a high ranking may become clearer.

DEBT LOAD

Debt load is one of the most difficult variables to analyze. In some studies, it has been found to be a significant factor when it is high, and therefore causes the student a considerable amount of anxiety\f\h [8,1]. It is a new trend that students are more likely to opt for higher paying careers in these instances, despite the fact that the residencies for these specialties tend to take longer[2]. This certainly seemed to be true in this study as more people chose clinical medicine and surgery, which typically lead to higher incomes than family practice, as their levels of debt rose.

In another study, however, less than four percent of physicians said that debt had a major influence on specialty choice[3]. About half of those who indicated that it did, though, also indicated that they had foregone some training because of it. This tends to support the idea that the pursuit of greater training with increased debt load is a relatively new trend. It is expected that this trend will continue due to the fact that debt loads are increasing while physicians' incomes are either remaining stagnant or are being cut[4].

It should be noted that the results seen in this study may not be typical of all medical schools across the country. One of the major reasons for this is that Dalhousie had the second highest medical school tuition in the country (after Memorial University of Newfoundland) in 1996 – 1997\f\h [12]. If it is indeed the case that schools with higher tuition fees tend to produce less family practitioners due to the increased levels of debt that result, one would expect that, in the near future, Ontario schools will see comparable drops due to the recent deregulation of tuition fees in that province. This remains to be seen.

Incidentally, the median debt load in this study was somewhere between $40,000 and $60,000 and most people claimed that their debt caused them at least a moderate level of anxiety. It has also been shown that debt has a significant influence on students with children (reference). But, since none of the respondents in this study had children, this factor can not be commented on here.

WORKING LOCATION

Two of the questions asked of the respondents were the population of town in which they desired to work and the proximity to a metropolitan center that they wished to live. In an attempt to understand the reasons for their choices, these responses were correlated with the population of their hometowns. It was found that only a weak correlation existed between these variables, with those whose hometown was relatively large being only slightly more likely to choose to work in and live close to a metropolitan center. The largest proportion of people stated that they would prefer to work in a city of between 50,000 and 200,000 people and live within one hundred kilometers of a metropolitan center. The proportion of people who chose these responses were 40% and 28%, respectively.

GENDER VARIATIONS

A number of variations were seen between males and females in the sample. Most notable among these were in the categories of career choice, income, debt load, and practice location. Each will be treated separately in this section.

CAREER CHOICE

Interestingly enough, there seemed to be some variation between males and females in the choice of careers. While both groups picked clinical medical specialties more often than any other career path, the males were much more likely

to pick an alternative specialty than were females. In fact, a much larger proportion of those who chose a surgical specialty were males (75%).

PRACTICE LOCATION

Another variation seen between males and females in this study was the desire to spend time practicing medicine outside of Canada. While most males (57%) said that they did not plan to spend any time practicing medicine in another country, only 32% of females stated that they had no plans of practicing medicine outside of Canada. The correlation coefficient for these variables was 0.44, or moderate.

DEBT LOAD

Males were more likely to have accumulated a higher debt load than were females. A large proportion of males fell into the debt range of $40,000 - $60,000 whereas many females fell into the lower range of $20,000 - $40,000. The correlation coefficient for this relation was 0.22.

INCOME

The greatest discrepancy between male and female expectations came in the category of expected level of income. Males were most likely to choose a level of income ranging from $160,001 - $250,000 whereas females were most likely to opt for the lower income range of $80,001 - $160,000. The correlation coefficient of 0.33 for this relation showed a moderate correlation between these variables. The reason for this may be due in part to the trend we saw earlier of higher debt loads corresponding to the pursuit of higher-paying specialties. Since there does not seem to be any information in the literature concerning this point, it is difficult to either confirm or deny this suspicion.

CONCLUSIONS

As stated above, this study represents the first step in the process of gathering data on the attitudes and expectations of graduating Canadian medical students toward their future. As a first step, it was relatively successful in achieving its goals. For instance, the survey was constructed, piloted, and refined to the point where it can be used as an effective tool for use in further steps. As well, the response rates were high enough to allow for relative reliance on the data obtained for Dalhousie Medical School as a reflection of the entire class of 1999. These results, however, cannot be used to draw conclusions on the characteristics of the other fifteen Canadian medical schools as situations in different provinces and, indeed, at different schools within a province may vary dramatically (e.g. with tuition and/or demographics). It is therefore necessary that representative samples be obtained from each school.

In future steps, it is recommended that more time be allotted for response to the survey than in this step. This would allow more of a chance to achieve greater response rates, thereby increasing the reliance on the data. As well, despite suspicions that certain variables were quite closely related, the correlation coefficients calculated with the data obtained here are not extremely high. It is suggested that more attention be given to the construction of some of the questions in order to enable a more effective correlation analysis for the remaining medical schools.

This is a study with potentially important implications for both the physicians already practicing medicine in Canada and those who will soon be entering the profession. It has been a learning process and some helpful insights have been gained with this step. The next step is to use the knowledge gained here to make appropriate changes to the process in order to ensure that the potential usefulness of this effort will be maximal.

ACKNOWLEDGEMENTS

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LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins.

Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG Co-A reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa),
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly-to-moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). Chylomicrons, which characterize Types I and V, have not been measured in clinical studies in patients with high TG levels (>11 mmol/L).

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

LDL-C (mmol/L) = total-C - [(0.37 x (TG) + HDL-C)]

LDL-C (mg/dL) = total-C - [(0.2 x (TG) + HDL-C)]

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

[1]Friedewald, WT et al. *Clin Chem* 1972; 18(6): 499-502.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of a pharmacokinetic study with erythromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors.

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Drug Interactions

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is no experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.

Oral Contraceptives: Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethindrone and 35µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (including erythromycin and clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), or the antidepressant nefazodone may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In a study with healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and erythromycin, a known inhibitor of CYP 3A4 (see WARNINGS, Muscle Effects).

Other Concomitant Therapy: In clinical studies, LIPITOR was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid-lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports of severe myopathy with or without rhabdomyolysis have been reported (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated cases of thrombocytopenia and allergic reactions (including urticaria, angioneurotic edema and anaphylaxis) that may have no causal relationship to atorvastatin, have also been reported.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the American Heart Association (AHA) Step 1 diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia

The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy.

Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of 4 weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

[a]Results are pooled from 2 dose-response studies.
[b]Mean baseline values.

Severe Dyslipidemias:

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions; Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

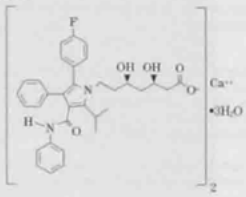
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg or 40 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 25°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

References:

1. Koren MJ, Smith DG, Hunninghake DB, *et al.* The cost of reaching National Cholesterol Education Program goals in hypercholesterolemic patients: A comparison of atorvastatin, simvastatin, lovastatin and fluvastatin. *Pharmacoeconomics* 1998;14:59-70. 2. LIPITOR (atorvastatin calcium) Product Monograph, Parke-Davis Div., Warner-Lambert Canada Inc., Dec. 1998. 3. Dart A, *et al.* A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol* 1997;80:39-44. 4. Bertolini S, *et al.* Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997;130:191-7. 5. Data on file. 6. ODB Formulary, Dec. 1998.

For a copy of the Product Monograph or full Prescribing Information, please contact:

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PrNORVASC*

(amlodipine besylate)

Brief Prescribing Information
NORVASC*
(amlodipine besylate)
Tablets 2.5, 5 and 10 mg
Antihypertensive-Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY

NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE

Hypertension

NORVASC (amlodipine besylate) is indicated in the treatment of mild-to-moderate essential hypertension.

NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. **NORVASC** can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of **NORVASC** with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina

NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. **NORVASC** may be tried in combination with beta-blockers in chronic stable angina, in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS

NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Impaired Hepatic Function

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. **NORVASC** should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Beta-blocker Withdrawal

NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS

Use in Patients with Congestive Heart Failure

Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that **NORVASC** had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Hypotension

NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema

Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Pregnancy

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with **NORVASC** in pregnant women. **NORVASC** should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, **NORVASC** should not be given to nursing mothers.

Use in Children

The use of **NORVASC** is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. **NORVASC** should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

Interaction with Grapefruit Juice

Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Co-administration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.

Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:

- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids

Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.

Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with **NORVASC**, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

Sildenafil: A single 100 mg dose of sildenafil (VIAGRA) in subjects with essential hypertension had no effect on AUC_t or C_{max} of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

Special Studies: Effect of **NORVASC** on other agents.

Atorvastatin: In healthy volunteers, co-administration of multiple 10 mg doses of **NORVASC** with 80 mg of atorvastatin resulted in no significant change in the AUC_t, C_{max} or T_{max} of atorvastatin.

ADVERSE REACTIONS

NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity.

Hypertension

In the 805 hypertensive patients treated with **NORVASC** in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):

Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina

In the controlled clinical trials in 909 angina patients treated with **NORVASC**, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%). The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):

Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** vision abnormal (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).

NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.

The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, peripheral neuropathy, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leucopenia, purpura, thrombocytopenia.

†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of **NORVASC** (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As **NORVASC** is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION

Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of **NORVASC** (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function

The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function

Dosage requirements have not been established in patients with impaired hepatic function. When **NORVASC** is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS

Availability

NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE

Store at 15-30°C. Protect from light.

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