REVIEW ARTICLE

# Primary Health Care Ethics in the Wake of the Human Genome Initiative.

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The Human Genome Initiative, or Human Genome Project, is an international collaborative effort to sequence the human genome. This will enable us to better understand genetic information and to apply this knowledge in the prevention or treatment of disease. Presently, and following the completion of the project, physicians in various fields of medicine will be required to possess the knowledge, skills and ethical demeanour to deal with genetic counselling, screening and testing of patients. It is obligatory that the medical community prepare for the increased ethical attentiveness that will be required of them in the face of this new genetic knowledge.

## INTRODUCTION

Few technological milestones can rival man's landing on the moon or harnessing the power of the atom, but the Human Genome Initiative promises to be just as remarkable. Historically, the Human Genome Initiative is the collective name for several projects begun in the late 1980s in several countries. It followed the United States Department of Energy's decision to create an ordered set of DNA segments from known chromosomal locations, develop new computational methods for analysing genetic map and DNA sequence data and generate new techniques and instruments for detecting and analysing DNA (1). The current phase of the Human Genome Initiative involves identifying and localizing the estimated 50,000 to 100,000 genes in the human genome by sequencing three billion base pairs on twenty-three chromosome couplets (2-4). Total costs are anticipated to be approximately three to five billion dollars (5) with expected completion in the year 2005 (2-6). The aim of the program is to increase our ability to predict, understand and eventually prevent or cure human diseases (6).

The Genome Initiative will provide us with the sequences of all human genes. Gene mutations are now known to play a role in many common human diseases, such as heart disease, diabetes mellitus, immune system disorders and cancer (6). Genetic diseases and congenital malformations occur in approximately 3-5% of all live births (7). There are about 3,000 medical disorders predicted to result from a single altered gene, with discoveries of the genes associated with specific disorders being announced almost monthly (7). Identifying genes unique to a disorder will make it possible to introduce more efficient screening programs for populations considered at risk. Furthermore, with increased understanding of the interaction between genes and the environment, we may be able to manipulate environmental factors early on (7), minimizing the development of genetically-determined illnesses.

It is imperative that the possible use or misuse of the project's findings be anticipated and addressed. To this end, the US National Institute of Health has allocated three percent of its budget for the Human Genome Initiative to bioethical analysis (8), making this the first scientific project that from its inception has incorporated a commitment to studying ethical, legal and social issues (9). The potential future ability to generate any individual's genetic profile raises important questions of privacy, confidentiality, ownership and autonomy. How should information be protected? Who should have

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access to the information and under what circumstances? What rights, if any, do employers, insurers and family members have to an individual's genetic information? Diagnosis of many genetic disorders will be possible before treatment becomes available. How will we resolve dilemmas raised by such a gap (3)? How might the Human Genome Initiative affect our concepts of 'disease,' 'normalcy' and 'humanness' (6)? Physicians must ponder how they will divulge potentially distressing genetic information to patients, how they will protect patients from the discrimination of interested third parties and how they will prepare and educate the community about the increasing role of genetics in medicine (5). Although all specialists will have to consider the impact of genetic information in their work, the issues will be encountered earliest and most frequently by family practitioners, obstetrician-gynaecologists and medical geneticists. It is therefore paramount that such primary care professionals be well-versed in the changes, especially increased ethical awareness and responsibility, that will take place in medical practice.

Physicians will not only be expected to be adept at performing genetic screening, but they will also necessarily become ethical gate-keepers. Genetic ailments affect millions of people worldwide who must live with their own version of the disease daily. Genetic screening and therapy may one day be commonplace in our arsenal against illness. Primary health care providers, as the first line of intervention, must learn how to manage the new genetic information arising from the Human Genome Initiative. This paper will discuss the pertinent ethical matters with which physicians will cope in this era of genetic advances, matters which will become more defined in the years following the completion of the Initiative.

## ETHICAL IMPLICATIONS FOR PRIMARY HEALTH CARE PROVIDERS

The concerns arising from genetic research are not new. What is novel is that the Human Genome Initiative is the first undertaking that raises all the ethical issues at once (5). Presently, genetic screening is available for a very limited number of diseases, including Down syndrome, Tay-Sachs disease and cystic fibrosis. But with the estimate that gene defects underlie 3,000 to 4,000 different diseases, not including polygenic etiologies, we are, as one author put it, "in a lull before a storm of information." (10) It is critical that national or even international agreement on principles guiding gene research and its clinical applications is reached before the Initiative makes its full impact on medicine. Moreover, it is not solely the responsibility of physicians to take charge of the ethical matters surrounding genetic advances. These issues impact on all of humanity and must be addressed by all. As intermediaries between technology and the patient, however, primary care physicians have a unique obligation to join in the consideration and debate of these issues (11). Existing genetic counselling services do not replace the necessity to explain the implications of a genetic test in the primary care setting (12, 13). All physicians must be educated in the science of clinical genetics and be aware of the moral issues surrounding the new technologies.

### *Classical ethical concerns related to the management of genetic information*

The most direct ethical implications for primary care physicians dealing with genetic consultations will be in the management of information. Issues in this arena concern voluntariness of the patient, coercion on the part of the health professional, maintenance of confidentiality, access to information by third parties, securing informed consent and upholding patient autonomy. Conventionally, health care ethics has distinguished between rights and duties, i.e. the rights of patients balanced against the duties of physicians. Patients' rights include the free and uncoerced authority to reach a decision (the principle of autonomy) and the right of consenting to medical care after disclosure of all the necessary information needed to reach a decision (fully informed consent). Physicians have traditionally been seen as protectors of the patient and have been guided by the duty of doing no harm to the patient (the principle of beneficence or non-maleficence). Although much philosophical debate has surrounded the rights-duties dyad, it is apparent that in every clinical situation, physicians must balance all ethical issues in striving to give the patient the best medical care they can.

### *Lack of physician readiness to manage genetic data: an ethical infringement*

Perhaps the most fundamental concern is the unpreparedness of physicians to meet the challenges that the new genetic technology will pose. Evidence suggests that several barriers exist to the adopting of genetic tests by physicians. These include lack of knowledge, inability to interpret probabilistic information, low tolerance for uncertainty, negative attitudes about their responsibility for genetic counselling and testing, lack of confidence in their clinical skills and unfamiliarity with ethical issues raised by testing (12). Physicians differ in their translation of test results, some claiming, for instance, that a risk of 1 in 2,500 for cystic fibrosis is "common" while others claim it is "rare" (12). It has also been reported that physicians sometimes intentionally misrepresent information to patients, including some related to screening (14). Studies have shown that there is a tendency to under-estimate the importance of unknown information and over-estimate what is known (15). In past surveys, many physicians have expressed negative attitudes towards additional training in genetics, favouring specialized counselling clinics instead (16). If many physicians lack confidence in their ability to

provide genetic tests and counselling, they are less likely to do so.

Important ethical ramifications stem from these 'barriers of unpreparedness.' If physicians possess inadequate knowledge and counselling skills regarding genetic testing, is it ethical for them to offer such tests? What obligations do they have to their patients in the face of uncertainty? In the new era of human genome research, without adequate training, non-geneticist physicians may not be able to define the benefits and burdens or to understand genetic testing. They will be unable to appeal to the principle of beneficence - acting in the patient's best interests. They will also be unable to appeal to the principle of patient autonomy, or right to make an uncoerced decision (12). Without a fully informed consent, autonomy is violated, since autonomy is the principle upon which informed consent is based. As well, unprepared physicians could undermine the validity of the process of informed consent by acting coercively or manipulatively (12). Moreover, if lack of knowledge, lack of confidence and low tolerance for uncertainty are, indeed, barriers to action, even appropriate, prudent and beneficial applications of genetic technology are likely to be withheld from patients who need it (12).

*Making ready - a professional obligation*

How can physicians prepare for this responsibility? Training for primary care practitioners is needed in the areas of human genetics and counselling patients before and after such testing. This could be integrated into residency program curricula, for example, via case conferences (13). An interesting idea proposed to solve the burden of genetic counselling is the development of computer-based interactive video programs to provide standardized patient-specific presentations (7). As well, clinical standards are needed to guide conduct for all physicians in the dissemination of genetic information. The Canadian College of Medical Geneticists, for instance, has adopted a code of standards on counselling (5).

Physicians, as holders and utilizers of the new genetic knowledge, must take an active role in educating the public about the implications of genetic testing and manipulation. The lay community should be made aware of their options regarding genetic testing in order to make decisions regarding personal lifestyle choices, as well as in considering reproductive alternatives. They must also be warned of the limitations - we cannot expect to cure all disease within twenty years and must not look upon genetic manipulation as a panacea for the world's woes (1). The importance of evaluating public values toward genetic testing is critical in appreciating patient response to future screening and in developing public policy (17).

## SIGNIFICANCE AND ETHICAL CONSIDERATIONS OF GENETIC TESTS

Issues of predictive value become important when considering the expanding array of genetic testing technologies (18). For particular tests to become professionally adopted, it will be necessary to establish minimum acceptable levels of sensitivity and specificity. Specificity is critical because a large number of false-positive test results produces extreme mental suffering for healthy persons who are told that they may develop serious genetic disorders (2) and may necessitate additional unnecessary investigations. Similarly, sensitivity is crucial because false-negative test results would give a mistaken sense of security to persons with genetically-based susceptibilities (2). Neither the ability nor the desire to change behaviour is distributed equally among all individuals. For example, individuals who are told they are not at a genetic predisposition to develop lung cancer may continue to smoke. This is problematic for two main reasons: the test results may be falsely-negative and the individual at stake may still develop lung cancer for non-genetic reasons. Many of us have an incorrect view of heritability - that genes are destiny. However, researchers are well aware that expression of the same genes in disparate environments may result in different outcomes and so lifestyle is just as pivotal a consideration as genetics with regards to the onset of many diseases. Physicians must, therefore, clearly communicate the uncertainty of test results and dispel the prevailing misconception of heritability to their patients. The same worries are held for home test kits for genetic testing (8).

*Eligibility of genetic ailments for screening and potential discrimination of those tested*

Because DNA analysis has the potential to provide so much information, it poses ethical problems about which genetic disabilities should be considered as candidates for prenatal diagnosis with the option for termination of pregnancy (17). What constitutes a serious genetic disability? Physicians will be called upon to counsel patients who want to terminate a pregnancy because they do not wish to bring a genetically disabled child into the world. Is a potential child with Down's syndrome a candidate for an abortion? Is it appropriate for society to decide that physical disability is always undesirable (17)? Traditionally, primary health care providers have embraced the merits of preventive medicine, especially for conditions which cannot be cured. In the sphere of human genetics, it is probable that we may eventually be able to correct genetic anomalies through somatic cell or germ-line genetic manipulation. Would it still be ethical to allow termination of pregnancies, in keeping with the view that in genetics, avoidance equals prevention? Society must

decide and medical professionals will be responsible for upholding society's values. History has seen the misuse of genetics during the eugenics movement and most will agree that sex selection or selection of desirable traits, such as height, are not criteria for stopping a pregnancy. Similarly, it will be very important that in our efforts to screen and avoid serious genetic disease we do not forget to pay enough attention to developing methods to treat these conditions. It is unlikely that we will be able to develop screening programs to cover all genetic disease. In any case, the widespread use of selective abortion should not be the ultimate goal of clinical genetics (17).

Physicians must also be wary of discrimination imposed on persons who have been given the label of a genetic disease. Social stigmatization is unlikely to be wholly erased but physicians must ensure that patients are not overcome by the bias of biological determinism that "we are our genes," which is simply not the entire story. Information improperly given can damage morale and self-esteem and alter important decisions (5). Particular genetic labels might have lasting effects on parent-child bonding, peer relationships, school performance and expectations and in adolescence, on career choices and life plans (11). Family physicians and pediatricians will be called on to explain and interpret the results of a multitude of tests to anxious parents and the manner in which this information is presented may permanently affect the parents' view of the child (11).

*Selection of candidates for genetic testing: issues of justice and resource allocation*

Issues of distributive justice emerge when the proposed costs of genetic counselling and intervention would keep certain members of society from using them. Testing may run to thousands of dollars per patient - for testing, physician visits, and genetic counselling (13). Thus, rationing such technologies may prove necessary. Future queries need to focus on which diseases will be tested for, which patients will be tested and what funds will be used (13). We should be aware that genetic prediction transfers accountability and responsibility for health to the individual, decreasing society's responsibility to eliminate the adverse social circumstances (8). This promotes a potentially coercive model of medicine, and may lead to 'victim blaming' of those who do not follow what is supposedly 'sensible' advice for their health. Physicians must be responsive to this and society as a whole must examine the claims of potential benefits versus harm (13).

*Attending to patients' psychosocial needs*

Psychological grief can ensue following disclosure of a genetic disease, especially if it is life-threatening or a cure is not available. Some patients may not want to know such information. Others who initially think that they desire such knowledge may change their minds after careful consideration of the consequences (2). Thus, an issue in divulgence of genetic information for physicians is a predisclosure discussion of ways that genetic information may affect patients' lives psychologically and socially, as well as economically (2). It would be an act of beneficence for physicians to do so. Furthermore, in the somewhat polarized fiduciary relationship that exists between physician and patient, sensitivity to such issues increases the patient's confidence and trust in the physician and the health care system, which is seen to look out for the whole patient, and not just his or her physical disorder. The Canadian Collaborative Study of Predictive Testing for Huntington's Disease (CCSPT) was launched in 1988 and included the participation of fourteen genetic centres from across the country, all following the same clinical research and protocol. After completing the first year of follow-up on participants in this study, it was found that there was little evidence to suggest that predictive testing for Huntington's disease had harmful effects on either the increased or decreased risk study groups (19). Moreover, no significant differences were found between the study groups with respect to the proportions of individuals who experienced severe psychological difficulties during the test follow-up period (20). The success of this trial should be a model for future genetic testing endeavours.

A not uncommon complication of genetic testing is the question of additional information which may be obtained as part of a genetic screening procedure, for example, a finding of non-paternity (17). When carrying out prenatal diagnosis by DNA analysis, particularly if genetic linkage is used, it is absolutely vital to determine the biological parentage of a fetus (17). Since non-paternity may lead to a mistaken prenatal diagnosis result, it is important to tell mothers as part of the counselling procedure that these tests will be valid only if parents are the true biological parents of the child (17). Perhaps physicians, when confronted with instances of non-paternity, are justified in breaking the general rule that all information found during genetic analysis should be disclosed.

*The right not to know*

Autonomy usually connotes the concept that patients ought to know as much as possible before making a decision. In existing genetic services, we recognize a right not to know our genes (1). What moral issues does the physician face in circumstances like this? Consider the following case:

> A newly married couple - a 24-year-old man and his 22-year-old wife - come to the family practice clinic to discuss their plans to have children. There is an extensive family history of cystic fibrosis. The physician suggests that the patients havegenetic tests for cystic fibrosis. The husband agrees but the wife adamantly refuses, saying "I just don't want to know." The physi-

cian's and husband's attempts at persuasion are ineffective. The wife reasons that the emotional consequences of such knowledge would be too burdensome on her marriage and her potential children's future (2).

Even though the wife in this case is certain she does not want to know about her genetic profile, it would not rule out the physician's duty to provide genetic counselling in which she is presented with information regarding the relative benefits and burdens of testing. For patients who are not as certain as the wife in this situation, physicians should be prepared to offer counselling that presents information regarding genetic testing in as neutral a manner as possible in keeping with health promotion goals (2). It would be beneficial to provide screening programs in family practice settings that offer an option for patients who simply "don't want to know" to refuse testing after appropriate discussion. This approach would not compromise the moral interests of patients with conscientious objections to acquiring genetic information (2).

*Maintaining positive intrafamily relationships*

Family members may not necessarily be cooperative or truthful in disclosing test results among themselves. The concept of a "family covenant" may help in highlighting the responsibilities of individuals within families and guide their interactions with their family physician (13). The family covenant is a patient care model that describes a contract between a family and physician in which boundaries may be set on the information family members divulge to each other as well as on that which the physician may discuss with individuals within the family (13). The decision not to share one's test results with others could involve privacy claims - a right not to have one's life interfered with by others. As well, it could entail confidentiality claims - that a physician caring for two family members has an obligation not to violate the confidence of one patient by disclosing information to the other. Such redefining of the physician-family relationship may become necessary with the advent of new genetic technologies.

## CONCLUSION

With the completion of the Human Genome Initiative, humanity will have reached a new and exciting frontier in the realm of understanding and conquering disease. Medical professionals will have to meet the demands of genetic testing, screening and manipulation by increasing their knowledge of genetics and their ethical awareness. They must meet the holistic needs of individuals, including the physical and also the emotional and economic concerns of patients. Society must be made aware that the prevailing responsibility is not a proximate one, but a long-term duty to future generations. In particular, we should not be blinded by the 'illusion of control' (18) the Human Genome Initiative will have over social problems. Physicians will have to renew their awareness of ethics and human psychology and agree upon policies that will guide the use of new genetic knowledge. Attention to such matters now, rather than later, will smooth the transition to the 'genetic era' and will enable humankind to benefit from forthcoming medical advances in genetics.

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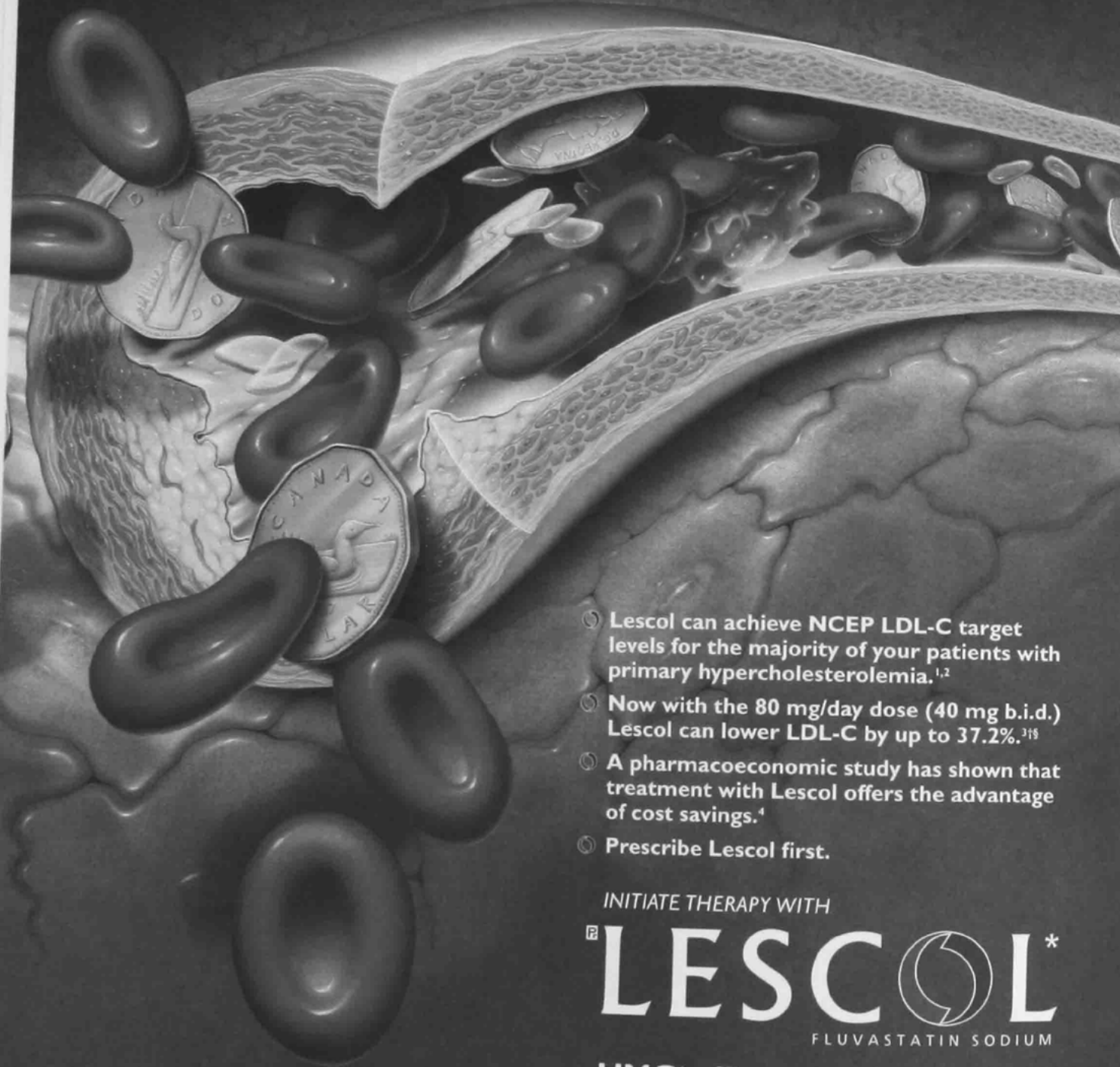


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Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of LESCOL, a lipid profile should be performed to measure Total-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 - HDL-C - 0.37 TG***.

For TG levels > 4.52 mmol/L (> 400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, as with other HMG-CoA reductase inhibitors, LESCOL is not indicated. Since the goal of treatment is to lower LDL-C, LDL-C levels should be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

LESCOL has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia Types I, III, IV, or V).

**CONTRAINDICATIONS:** Hypersensitivity to any component of this medication. LESCOL (fluvastatin sodium) is contraindicated in patients with active liver disease or unexplained, persistent clinically relevant elevations in serum transaminases (see WARNINGS).

As with other drugs of this class, LESCOL is contraindicated during pregnancy and in nursing mothers (see PRECAUTIONS).

**WARNINGS: The effect of fluvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality, or total mortality has not been established.**

**1. Hepatic Effects:** Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents.

Overall, 25 of 2373 patients (1.1%) treated with LESCOL in worldwide controlled clinical trials developed marked persistent elevations (to more than 3 times the upper limit of normal) in transaminase levels requiring discontinuation of treatment in 14 (0.6%) patients. The incidence of such elevations varied from 0.9% at 20 mg/day to 1.9 % at 80 mg/day.

In all clinical trials (controlled and uncontrolled), ranging from 28 to 71.2 weeks of exposure, 33 of 2969 (1.1%) patients had persistent transaminase elevations requiring discontinuation of treatment in 19 (0.6%) patients. In the majority of patients, these abnormal biochemical findings were asymptomatic.

**It is recommended that liver function tests be performed at baseline and 12 weeks after initiation of treatment as well as after an increase in the dose, and periodically thereafter.** Particular 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 the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued.**

LESCOL 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 LESCOL; if such conditions develop during therapy, the drug should be discontinued.

**2. Muscle Effects: CPK:** Transient elevations of creatine phosphokinase (CPK) levels have been seen in fluvastatin-treated patients but have usually been of no clinical significance.

**Myalgia** and muscle cramps have also been associated with fluvastatin therapy.

**Myopathy** has been reported in isolated cases with LESCOL. Two cases were in patients receiving placebo. The incidence of myopathy in LESCOL-treated patients compares favorably with that in placebo.

Myopathy should be considered in patients with diffuse myalgias, muscle tenderness or weakness and/or marked elevations of creatinine phosphokinase (10 times the upper limit of normal). Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with other drugs of this class. Rhabdomyolysis has been reported in isolated cases with LESCOL.

An increased risk of myopathy has been reported with HMG-CoA reductase inhibitors when administered concomitantly with immunosuppressive drugs, including cyclosporine, gemfibrozil, erythromycin, or niacin.

**Therefore, the benefits and risks of using HMG-CoA reductase inhibitors concomitantly with immunosuppressive drugs, erythromycin, fibrates or lipid-lowering doses of niacin should be carefully considered.**

There is limited experience to date with the use of LESCOL together with cyclosporine. In a study conducted in 19 stable renal transplant patients receiving cyclosporine A concomitantly with fluvastatin 20 mg/day, the AUC for fluvastatin was increased by 1.9 times (94%). Published data indicate that the trough concentration of cyclosporine A was not changed.

At present, since no data with doses above 40 mg/day are available, this dosage should not be exceeded in patients receiving cyclosporine A.

Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with LESCOL together with niacin.

The use of fibrates alone or in combination with HMG-CoA reductase inhibitors has been occasionally associated with myopathy. In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and LESCOL at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate.

**Interruption of therapy with LESCOL should be considered in any patient with an acute serious condition suggestive of myopathy or having a risk factor predisposing to the development of renal failure or rhabdomyolysis, such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.** Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

**PRECAUTIONS: General:** Before instituting therapy with LESCOL (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of LESCOL or any other lipid-lowering agent.

**Homozygous Familial Hypercholesterolemia:** LESCOL (fluvastatin sodium) has not been evaluated in patients with rare homozygous familial hypercholesterolemia. HMG-CoA reductase inhibitors are reported to be less or not effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have no or very little LDL receptor activity. Additionally, studies with other HMG-CoA reductase inhibitors indicate that such treatment appears more likely to raise serum transaminases in these homozygous patients. For heterozygous familial hypercholesterolemia (FH) optimal reduction in total and LDL cholesterol necessitates combination drug therapy in the majority of patients.

**Effect on Lipoprotein(A)[Lp(a)]:** In some patients the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with LESCOL.

**Effect on $CoQ_{10}$ levels (ubiquinone):** A significant decrease in plasma $CoQ_{10}$ levels in patients treated with LESCOL and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of $CoQ_{10}$ has not yet been established.

**Renal Impairment:** Because LESCOL does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal impairment.

As there is no experience with LESCOL in patients with severe renal insufficiency (creatinine > 260 µmol/L, i.e. creatinine clearance < 30 mL/min), its use cannot be recommended in this patient population.

**Endocrine Function:** HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such could theoretically blunt adrenal and/or gonadal steroid production.

LESCOL exhibited no effect upon non-stimulated cortisol levels, FSH (males only) or thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with LESCOL 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.

**Effect on Lens:** Current data from long-term clinical trials do not indicate an adverse effect of LESCOL on the human lens.

**Pregnancy: LESCOL is contraindicated during pregnancy** (see CONTRAINDICATIONS). Data on the use of LESCOL in pregnant women is limited. A few reports have been received of congenital anomalies in infants whose mothers were treated during a critical period of pregnancy with other HMG-CoA reductase inhibitors. During the clinical program, a total of 5 women who were receiving LESCOL became pregnant and were discontinued from the studies. Of these 5 women, 3 gave birth to healthy babies, one experienced an ectopic pregnancy which was attributed to a severely scarred fallopian tube and one spontaneously aborted.

Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators 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 fetal harm when administered to pregnant women.

LESCOL 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 this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus (see CONTRAINDICATIONS).

**Nursing Mothers:** It is not known whether LESCOL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from LESCOL, women receiving LESCOL should not breast-feed (see CONTRAINDICATIONS).

**Pediatric Use:** Limited experience with the use of other HMG-CoA reductase inhibitors is available in children. Safety and effectiveness of LESCOL in children have not been established.

**Geriatric Use:** The effect of age on the pharmacokinetics of LESCOL was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender.

**DRUG INTERACTIONS: Concomitant Therapy with other Lipid Metabolism Regulators.**

**Combined drug therapy should be approached with caution as information from controlled studies is limited.**

A drug interactive effect (pharmacokinetic and/or clinical) has been shown for the following drugs in combination with LESCOL:

**Cholestyramine:** The cholesterol-lowering effects of LESCOL and the bile acid sequestrant, cholestyramine, are additive. Administration of LESCOL concomitantly 2 to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for the fluvastatin AUC and 50-80% for the fluvastatin $C_{max}$. However, administration of LESCOL 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing Total-C and LDL-C compared with that achieved with either component drug. (See DOSAGE AND ADMINISTRATION).

**Gemfibrozil/Fenofibrate/Niacin:** Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency (see WARNINGS: Muscle Effects). LESCOL has been safely administered concomitantly with nicotinic acid, gemfibrozil and bezafibrate in clinical studies. In short-term studies involving a small number of patients, myopathy was not reported during administration of bezafibrate and LESCOL at doses of 40 mg/day and 60 mg/day. To date, the 80 mg/day dose has not been evaluated with bezafibrate.

**Cimetidine/Ranitidine/Omeprazole:** Concomitant administration of LESCOL with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin $C_{max}$ (43%, 70% and 50%, respectively) and AUC (24 to 33%), with an 18 to 23% decrease in apparent oral plasma clearance (Cl/F).

**Digoxin:** In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of LESCOL had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin $C_{max}$ and urinary clearance were noted.

**Rifampicin:** Administration of LESCOL to subjects pretreated with rifampicin results in significant reduction in $C_{max}$ (59%) and AUC (51%) of fluvastatin, with a large increase (95%) in plasma clearance.

In pharmacokinetic studies and in retrospective analysis of the concomitant medications used during clinical studies, LESCOL did not show an interactive effect with the following drugs:

**Antipyrine:** Administration of LESCOL does not influence the metabolism and excretion of antipyrine, either by induction or inhibition. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system); therefore, interactions with other drugs metabolized by this mechanism are not expected.

**Beta-Adrenergic Blocking Drugs:** Concomitant administration of LESCOL with propranolol has no effect on the bioavailability of fluvastatin sodium.

**Warfarin:** *In vitro* protein binding studies demonstrated no interaction at therapeutic concentrations. In a drug interaction

study, the concomitant use of LESCOL and warfarin did not alter the plasma levels and prothrombin times compared to warfarin alone. However, since other drugs of this class have been shown to enhance the anticoagulant effect of warfarin, caution is advised when administering warfarin concomitantly with LESCOL.

**Other Concomitant Therapy:** Although specific interaction studies were not performed with all drugs listed below, in clinical studies, LESCOL was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, oral sulphonylureas, antacids, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant interactions.

Although no conclusive studies have been done to date with LESCOL, interactions with the following drugs have been reported with other HMG-CoA reductase inhibitors:

**Immunosuppressive Drugs, Erythromycin:** (See WARNINGS: Muscle Effects).

**LABORATORY INTERACTIONS:** The HMG-CoA reductase inhibitors may cause elevation of creatinine phosphokinase and transaminase levels (see WARNINGS). In the differential diagnosis of chest pain in a patient on LESCOL, cardiac and noncardiac fractions of these enzymes should be determined.

**ADVERSE REACTIONS:** In all clinical studies (controlled and uncontrolled), 1% (32/2969) of LESCOL patients were discontinued due to adverse experiences attributed to study drug (mean exposure of approximately 16 months ranging in duration from one to more than 36 months). This results, in controlled studies, in an exposure adjusted incidence of 0.8% per patient year in fluvastatin patients compared to an incidence of 1.1% in placebo patients. Adverse events were usually mild and transient. Clinical adverse reactions of positive or uncertain relationship to study medication occurring at a frequency ≥ 1% in controlled clinical trials with LESCOL are listed below.

| | Lescol | | | Placebo |
|---|---|---|---|---|
| **Adverse Event** | **20 mg/d (N = 1425) %** | **40 mg/d (N = 1136) %** | **80 mg/d (N = 369) %** | **(N = 960) %** |
| **Gastrointestinal** | | | | |
| Dyspepsia | 4.7 | 4.8 | 7.3 | 2.3 |
| Constipation | 2.8 | 1.8 | 2.4 | 2.5 |
| Abdominal pain | 2.7 | 2.1 | 3.8 | 2.0 |
| Flatulence | 2.5 | 1.9 | 1.6 | 2.2 |
| Diarrhea | 2.5 | 1.5 | 1.6 | 2.1 |
| Nausea | 2.0 | 1.6 | 0.8 | 1.4 |
| Eructation | 1.4 | 0.6 | 0.5 | 1.1 |
| **Musculoskeletal** | | | | |
| Myalgia | 1.7 | 1.8 | 2.7 | 2.3 |
| Arthralgia | 1.4 | 1.4 | 1.4 | 1.5 |
| Back pain | 1.0 | 0.8 | 1.1 | 1.6 |
| **Central nervous system** | | | | |
| Dizziness | 0.9 | 1.1 | 0.5 | 1.8 |
| Abnormal vision | 1.0 | 0.9 | 1.1 | 1.4 |
| **Psychiatric** | | | | |
| Insomnia | 1.9 | 1.3 | 0.3 | 0.9 |
| **Respiratory** | | | | |
| Upper respiratory infection | 1.1 | 0.9 | 2.4 | 1.9 |
| **Integumentary** | | | | |
| Rash | 1.5 | 0.8 | 1.9 | 1.6 |
| **Miscellaneous** | | | | |
| Headache | 3.8 | 2.7 | 1.9 | 3.0 |
| Fatigue | 1.8 | 1.5 | 0.5 | 1.8 |
| Chest pain | 0.3 | 0.9 | 1.4 | 0.5 |

Other clinical adverse reactions of positive or uncertain relationship to study medication occurring in 0.5% to 1.0% of patients receiving 20-80 mg LESCOL monotherapy in controlled clinical trials ($N = 2326$) are listed below:

**Gastrointestinal:** Vomiting, gastritis.

**Musculoskeletal:** Arthritis.

**Central Nervous System:** Conjunctivitis, paresthesia.

**Respiratory:** Rhinitis.

**Integumentary:** Pruritus.

**Miscellaneous:** Leg pain, influenza-like symptoms, allergy.

**The following effects have been reported with drugs of this class:**

**Skeletal:** Myopathy, rhabdomyolysis (see WARNINGS), muscle cramping/pain.

**Neurological:** Paresthesia, peripheral neuropathy, psychiatric disturbances/anxiety.

**Hypersensitivity Reactions:** An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors and has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiform, including Stevens-Johnson syndrome.

**Gastrointestinal:** Hepatitis, cholestatic jaundice, anorexia, vomiting.

**Skin:** Alopecia.

**Miscellaneous:** Asthenia, sweating, hot flushes.

**DOSAGE AND ADMINISTRATION:** Prior to initiating LESCOL (fluvastatin sodium), the patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association [AHA] Step 1 Diet), which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented.

The recommended starting dose is 20 mg once daily to be taken in the evening or at bedtime. The recommended dosing range is 20-80 mg/day. The daily dose regimen of 80 mg should be administered in divided doses, i.e. 40 mg b.i.d. LESCOL should be taken with or after meals. Since the maximal reductions in LDL-C are seen within 4 weeks of administration of a given dose, periodic lipid determinations should be performed with dosage adjusted to a maximum of 40 mg twice a day, according to the patient's response.

The therapeutic effect of LESCOL is maintained with prolonged administration.

**Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LESCOL if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP).**

**Concomitant Therapy:** The lipid lowering effects of LESCOL on total cholesterol and LDL cholesterol are enhanced when combined with a bile-acid binding resin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium concomitantly, LESCOL should be administered at bedtime, at least 4 hours following the resin to obtain a maximal lipid lowering effect. (See PRECAUTIONS, DRUG INTERACTIONS).

**Dosage in Patients with Renal Insufficiency:** Since LESCOL is cleared hepatically with less than 5% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not deemed to be necessary. Caution should be exercised with severe renal impairment (see PRECAUTIONS).

**AVAILABILITY OF DOSAGE FORMS: LESCOL Capsules 20 mg** – Each brown opaque cap and light brown opaque body gelatin capsule contains 20 mg fluvastatin (from 21.06 mg fluvastatin sodium). Sandoz Triangle ⚠ printed twice and "20" in white ink on the cap; "LESCOL" and product logo in red ink on the body. Available in bottles of 100.

**LESCOL Capsules 40 mg** – Each brown opaque cap and gold opaque body gelatin capsule contains 40 mg fluvastatin (from 42.12 mg fluvastatin sodium). Sandoz Triangle ⚠ printed twice and "40" in white ink on the cap; "LESCOL" and product logo in red ink on the body. Available in bottles of 100.

**STABILITY AND STORAGE RECOMMENDATIONS:** Store between 15 and 30°C in a tight container. Protect from light and humidity.

**References: 1.** Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269(23):3015-23. **2.** National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey III (NHANES III). (Unpublished data). **3.** Lescol Product Monograph. Sandoz Canada Inc. **4.** Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clin Ther* 1994;16(6):1052-62.

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