Health Canada has recently approved the first anti-PCSK9 drug, called REPATHA™. There has been quite a lot of media attention on this new class of biologic drugs and it may have caused some concern for private drug plan managers given the high volume of their plan members who are already using cholesterol lowering medications, such as statins like Lipitor® or Crestor® or their generic counterparts.

It is understandable that drug plan managers may have concerns about the potential impact of the anti-PCSK9 category of drugs on their plans; however it is important to review and understand the Health Canada approved indicated patient population, to truly determine the impact on private drug plans. Statins are commonly used to treat hypercholesterolemia or high cholesterol as a first line therapy, whereas the anti-PCSK9 drugs are indicated for patients who are at high risk for a secondary cardiovascular event such as a heart attack or stroke and cannot reach the Canadian LDL (low-density lipoprotein known as “bad” cholesterol) target despite treatment with maximally tolerated statin therapy. These patients have severe disease and have fewer treatment alternatives.

On September 10, 2015, Health Canada approved REPATHA™ for patients with the following conditions:

**Primary Hyperlipidemia**

REPATHA™ is indicated as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

The effect of REPATHA™ on cardiovascular morbidity and mortality has not been determined.
**Homozygous Familial Hypercholesterolemia**

REPATHA™ is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in adult patients and adolescent patients aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

This approval means that REPATHA™ is recommended ONLY for the following kind of patients:

1. **Patients with clinical atherosclerotic cardiovascular disease (ASCVD)** (who are not at goal despite maximally tolerated dose of statins)

2. **Patients with familial hypercholesterolemia (FH)** (have an inherited disorder which predisposes them to abnormally high levels of LDL-C and therefore increases risk of atherosclerotic cardiovascular disease)

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**Clinical atherosclerotic cardiovascular disease (ASCVD)**

According to the “official” guidelines:

*Clinical ASCVD is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin).”

Let’s examine each of the approved conditions in more detail:

**TABLE 1: Clinical Atherosclerotic Cardiovascular disease (ASCVD) Condition Descriptions**

<table>
<thead>
<tr>
<th>Clinical Term</th>
<th>Description</th>
<th>Laymen’s Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>• An umbrella term for situations where the blood supplied to the heart muscle is suddenly blocked.</td>
<td>Heart attack or unstable angina</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>• Damaging or death of an area of the heart muscle resulting from a blockage in the blood supply to that area.</td>
<td>Heart attack</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>• Unstable angina is chest pain that happens suddenly and becomes worse over time. It occurs seemingly without cause—you may be at rest or even asleep. An attack of unstable angina may lead to a heart attack.</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>• Predictable chest discomfort that occurs during physical exertion or under mental or emotional stress.</td>
<td></td>
</tr>
<tr>
<td>Coronary or other arterial revascularization</td>
<td>• Bypass surgery that improves the blood flow to the heart muscle.</td>
<td>Coronary artery bypass surgery</td>
</tr>
</tbody>
</table>
| Stroke                               | • Sudden loss of brain function. It is caused by the interruption of flow of blood to the brain (ischemic stroke) or the rupture of blood vessels in the brain (hemorrhagic stroke).  
  • The interruption of blood flow or the rupture of blood vessels causes brain cells (neurons) in the affected area to die. Can impact any number of areas including your ability to move, see, remember, speak, reason and read and write. |                                |
| Transient ischemic attack (TIA)      | • When a clot stops blood from flowing to the brain for a short time.         | Mini-stroke                    |
| Peripheral arterial disease (PAD)    | • When the arteries in the pelvis, legs or arms become narrow or blocked. Leads to cramping muscular pain while walking or during exercise  
  • May also affect the arteries supplying blood to the head, kidneys or stomach, increasing the risk for a stroke and organ damage respectively  
  • If the blockage remains in the peripheral arteries in the legs, it can cause pain, changes in skin color, sores or ulcers and difficulty walking. Total loss of circulation to the legs and feet can cause gangrene and loss of a limb.  
  If the blockage occurs in a carotid artery, it can cause a stroke. |                                |
Secondary prevention means preventing further attacks of CVD after the first attack has occurred, versus primary prevention, which is preventing a disease from occurring, so in CVD, this is preventing the blockage of arteries that bring blood to the heart (coronary artery disease). According to the guidelines in order to be diagnosed with clinical atherosclerotic cardiovascular disease patients have actually suffered from one of the following, (NOT just be at risk for): acute coronary syndrome (heart attack or unstable angina), myocardial infarction (heart attack), unstable angina, stable angina, coronary or other arterial revascularization (bypass surgery), stroke, transient ischemic attack (TIA) (mini stroke) or peripheral arterial disease (PAD). For more details on these conditions, see Table 1.

Dr. Jacques Genest, is a cardiologist at the McGill University Health center (MUHC), Professor of Medicine and Genetics at McGill University and for the past 16 years participated in the elaboration of Canadian Cholesterol Guidelines. Dr. Genest explains the indication: “REPATHA™ is not intended for primary prevention, which is preventing a first event, such as a heart attack or stroke—or any manifestation of ASCVD, but rather as secondary prevention where we would like to prevent a subsequent event from occurring, for example, a patient who has already suffered from at least one serious event. These patients are at a much higher risk for another cardiovascular event.”

Familial hypercholesterolemia
Familial Hypercholesterolemia (FH) is an inherited disorder that leads to aggressive and premature cardiovascular disease (CVD). In FH patients, genetic mutations make the liver incapable of metabolizing (or removing) excess low-density lipoprotein (LDL), known as “bad” cholesterol. The result is very high LDL levels which can lead to premature CVD.

FH is a serious condition that goes beyond high cholesterol resulting from poor diet and lifestyle choices and requires more aggressive treatment. Certain ethnic groups are more susceptible to having FH, such as people with Lebanese, French Canadian, Ashkenazi Jewish and South African Afrikaner backgrounds. If left untreated, people with FH have up to twenty times the risk of developing early aggressive heart disease.

There are two forms of FH.

1. Patients who have inherited this genetic mutation from one parent, have Heterozygous FH (HeFH).

HeFH occurs in 1 in 250 in the province of Quebec and 1 in 500 people in the rest of Canada.

2. Patients who inherit FH from both parents have Homozygous FH (HoFH), which is much more severe in its consequences. HoFH is very rare, occurring in about one in one million people in Canada.

HoFH leads to aggressive atherosclerosis, (narrowing and blocking of blood vessels). It begins before birth and progresses rapidly. It can be diagnosed with visual symptoms, such as xanthomas (bumps or lumps in the skin which are deposits of excess fat) and corneal arcus (white arc near the colored part of the eye). If left untreated, heart attack or sudden death can occur as early as the teen years.

Optimizing current treatment
According to Health Canada, REPATHA™ should be used as “an adjunct to diet and maximally tolerated statin therapy in patients with HeFH or ASCVD”. According to Dr. Genest, many patients are either undertreated, not treated, not adherent, or experiencing side effects with current treatments. He explains “it is essential that patients are optimized on traditional therapy (such as statins or ezetimibe) before considering anti-PCSK9 treatments.”

According to Durhane Wong-Rieger, Coordinator, FH Canada Patient Network “While some FH patients may be able to manage their condition, many have maximized existing treatments and made the necessary lifestyle changes and find their LDL still at a high risk level. Anti-PCSK9 medications should initially be available to those who are at high risk for cardiovascular event not because they are intolerant of or not responsive to current therapies; they are not a replacement for statins.”

There are some patients who have such severe disease that they may require lipoprotein apheresis, which is a weekly or biweekly procedure that involves blood cleansing with a special machine that looks like a dialysis machine. It is these patients that Health Canada is referring to when they say REPATHA™ should be used with “patients aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.”

What is the actual risk?
So in reality how many Canadian patients could potentially be treated with an anti-PCSK9 like REPATHA™? Let’s take a closer look:
TABLE 2: Mapping therapeutic unmet need (per 100,000 privately insured lives)

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Diagnosis</th>
<th>Unmet need</th>
</tr>
</thead>
<tbody>
<tr>
<td>~7%</td>
<td>~3%</td>
<td>~1%</td>
</tr>
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</table>

6,487 patients are at high risk and are on a statin

200 patients have HeFH

2,206 have been diagnosed with ASCVD (all ASCVD patients are high risk)

30 have been diagnosed with HeFH

1,308 on therapy, NOT at LDL-C target level and have ASCVD

1,324 on therapy, NOT at LDL-C target level and have HeFH

Clinical atherosclerotic Cardiovascular disease (ASCVD) + Heterozygous Familial Hypercholesterolemia (HeFH)

Therapeutic unmet need describes those patients who are currently being treated and whose LDL-C is NOT reaching target levels despite treatment and require alternative treatment.

Approximately 1% of privately covered lives have ASCVD or HeFH and despite therapy are not at reaching LDL-C target levels.

These patients are remain at a high risk of experiencing a cardiovascular event.

According to analysis, out of a pool of 100,000 private payer lives there is a possibility of 1,324 patients who would be eligible for REPATHATM based on its current indications. (Since occurrence of HoFH is very rare, with approximately 35 patients in Canada, these patients are not included in this analysis.)

Based on this projected eligibility and assumptions of market penetration over the first three years in the market, a budget impact analysis conducted by Amgen for Canadian insurance carriers determined that based on the Canadian list price, at a cost of $7,263.36 per patient, the cost of covering REPATHATM for a private drug plan of 100,000 lives would result in an incremental cost of $0.17 in Year 1, $0.49 in Year 2, and $0.98 in Year 3 per covered life per month.

With effective prior authorization to ensure that only appropriate patients are reimbursed for treatment, plan sponsors can ensure that the risk is managed and that their plan can provide coverage to plan members and their families who truly need this treatment.

REFERENCES

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