



Common Drug Review *Patient Group Input Submissions*

rifaximin (Zaxine) for Hepatic Encephalopathy

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.

Canadian Liver Foundation — permission granted to post.

Consumer Advocare Network — permission granted to post.

Gastrointestinal Society — permission granted to post.

HepCBC Hepatitis C Education and Prevention Society — permission granted to post.

CADTH received patient group input for this review on or before August 28, 2014

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Canadian Liver Foundation

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Rifaximin (brand name: Zaxine)
Name of the patient group	Canadian Liver Foundation
Name of the primary contact for this submission:	[REDACTED]
Position or title with patient group	[REDACTED]
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Name of author (if different)	
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Website	www.liver.ca
Permission is granted to post this submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

1.1 Submitting organization

When it was founded in 1969, the Canadian Liver Foundation (CLF) was the first organization in the world dedicated to supporting education and research into all forms of liver disease. Today, the CLF continues to be the only national organization committed to reducing the incidence and impact of liver disease for Canadians of all ages living with or at risk of liver disease. The CLF is the sole lay organization in Canada directing funds specifically for liver disease research and has invested more than \$20 million in the scientific search for causes, preventative measures and potential treatments for liver disease, including viral hepatitis. As the largest community organization dedicated to liver disease, the CLF reaches over 250,000 Canadians through our public and professional education programs, patient support programs and other fundraising and outreach efforts. Over the past 40+ years, the CLF has invested more than \$50 million in health education and prevention programs.

1.2 Conflict of interest declarations

- a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:
In the past, the Canadian Liver Foundation has received unrestricted educational grants and/or has worked on joint initiatives with AbbVie Corporation, Astellas Pharma Canada Inc., Boehringer Ingelheim (Canada) Inc., Gilead Sciences Canada Inc., Janssen Inc., Merck Canada Inc., Novartis Pharmaceuticals Canada Inc. and Hoffmann-La Roche Limited.

- b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:
Dr. Sherman, Chairperson of the Canadian Liver Foundation, has received honoraria from Abbvie Corporation, Boehringer Ingelheim (Canada) Inc., Merck Canada Inc., Janssen Inc., Hoffmann-La Roche Limited, Gilead Sciences Canada Inc., Vertex and Bristol Myers Squibb.

2. Condition and Current Therapy Information

2.1 Information gathering

In order to gather a broad range of input, the CLF invited patients, caregivers and health care professionals from across Canada to fill out an online survey modelled on the CADTH questionnaire. The survey was made available for two weeks and 24 responses were received. Quotes from survey respondents are included in italics in various sections of this submission. Other information was provided by CLF Chairperson Dr. Morris Sherman and Dr. Christopher Rose, Co-Chair of the CLF's Research Grant Committee and a research expert in the field of hepatic encephalopathy.

2.2 Impact of condition on patients

When a patient has advanced liver disease, the ailing liver is unable to clear the body of toxins which consequently build up in the brain causing neurotoxicity. This condition, defined as hepatic encephalopathy (HE), is a common and debilitating neuropsychiatric complication of liver disease. Characterized by a variety of symptoms affecting patients' ability to think, function and move, HE can progress to coma and death. HE is classified into two primary forms: overt HE (OHE) and minimal HE (MHE). A patient with OHE exhibits clearly identifiable signs such as arm flapping (known as 'asterixis'), stupor, seizures and coma, whereas a patient with MHE may have no overt or obvious symptoms of HE but is diagnosed using sensitive neuropsychological and neurophysiological tests. MHE is characterized by decreased concentration, poor memory, reduced speed of information processing, impaired motor abilities, increased risk of having a car accident, and disturbances in sleep-wake rhythms. These symptoms have a significant impact on patients' quality of life and on their ability to function daily.

"...when this happens, I am unable to do anything for myself, unable to remember my name, what day it is, not able to take my insulin or to do anything. The symptoms have really reduced my quality of life." – HE patient

"Confusion and inability to concentrate or remember anything new means I am no longer able to work or study." – HE patient

Liver specialists treating patients with hepatic encephalopathy report that patients suffer irritability, long-term learning and developmental difficulties, altered sleep/wake cycles, changes in personality and increased drowsiness (also known as 'somnia'). Patients often require repeated and prolonged hospitalizations due to the symptoms of hepatic encephalopathy.

"Patients typically present with problems related to memory, sleep and concentration which eventually progresses to severe forms with severe confusion, somnolence and even coma. In many of my patients, this can be insidious with minimal warning unless close family members notice something has changed. The impact on productivity and quality of life is immense and many patients become quite debilitated by HE." – physician treating HE patients

2.3 Patients' experiences with current therapy

Lactulose is currently the first-line treatment for OHE but it causes significant side effects, including gas, bloating, abdominal pain, flatulence and diarrhea. Due to necessary dosage adjustments, compliance can be a problem leading to recurring episodes of HE when patients do not take their medication properly. In addition, not all patients respond to lactulose.

"I cannot use lactulose alone because I have to take such a large doses that it caused severe diarrhea and that causes a loss of sodium and potassium which means I have to be admitted to hospital." – HE patient

"Current treatments are moderately effective (i.e. lactulose) but have considerable side effects. The gas, bloating, abdominal pain, and diarrhea are very poorly tolerated by patients, many of whom are non-compliant because of these side-effects. Approximately 10-15% of patients will not respond to this therapy." – physician treating HE patients

2.4 Impact on caregivers

The responsibility for caring for patients with HE often falls upon spouses, adult children or parents. It is very stressful as patients with HE can experience personality changes and mood swings as well as confusion and memory loss. Patients are often unable to work thereby making them financially dependent upon caregivers and/or social assistance.

"My mom suffered from HE and she became shaky and slow at first but later because of the HE she resembled someone with dementia to the point where she could not follow simple commands such as to stand or sit or eat. All she wanted to do was sleep and be left alone. This resulted in my dad having to have homecare for several hours of day and eventually have her placed in Long Term Care where she could get round the clock nursing care. In order to do simple things like getting groceries, my dad needed to have someone stay with her so she could be safe in her environment." – daughter of HE patient

3. Information about the Drug Being Reviewed

3.1 Information gathering

As mentioned previously, the CLF invited patients, caregivers and health care professionals from across Canada to fill out an online survey modelled on the CADTH questionnaire. The survey was made available for two weeks and 24 responses were received. Quotes from survey respondents are included in italics in various sections of this submission. Other information was provided by the CLF's Chairperson, Dr. Morris Sherman and Dr. Christopher Rose, Co-Chair of the CLF's Research Grant Committee and a research expert in the field of hepatic encephalopathy.

3.2 What are the expectations for the new drug or what experiences have patients had with the new drug?

Through the manufacturer's compassionate supply program and/or Health Canada's special access program, a number of patients have been taking rifaximin alone or in combination with lactulose. Both HE patients and physicians caring for HE patients report a dramatic improvement with the use of rifaximin. Patients regain their cognitive abilities and are able to be discharged from the hospital and return home with few, if any, recurrences of symptoms. Rifaximin effectively manages and/or prevents

episodes of OHE and therefore reduces hospital readmissions. Although more expensive (per treatment) than lactulose, rifaximin has been shown to be more cost-effective as patients spend less time in the hospital. Furthermore, patients report that rifaximin is easy to use (2 pills per day) and has minimal side effects.

“Only positive effects that I've noticed. Prior to using, I was admitted to hospital with severe hepatic encephalopathy, extreme confusion etc. It is easy to use, I just add it to my daily regime of medications. In the long term, it seems to control the symptoms, though still have some difficulty thinking straight.” – HE patient

“It is absolutely an amazing drug that has allowed me to return to life. I used to be hospitalized about every two weeks for a week or longer -- now I haven't been to the hospital since starting the drug nearly two years ago and have returned to full time work.” – HE patient

“Rifaximin was like a miracle to mom. Once administered it worked with the lactulose and allowed her to be stronger neurologically as well as to be clear headed. She was in hospital in November 2013 and did not have to be readmitted until June 2014. At this time, her admittance was not due to HE.” – daughter of HE patient

“Patients easily tolerated this medication and we did not notice increased side effects. The biggest noticed benefit was that many of my patients were kept out of the hospital. Patients with debilitating HE were able to have improved quality of life and well being by reducing the severity of their symptoms and keeping them at home.” – physician treating HE patients

4. Additional Information

Hepatic encephalopathy (HE) is a debilitating and potentially life-threatening consequence of cirrhosis and advanced liver disease. Patients suffering from many different forms of liver disease are at risk of developing HE and its symptoms can render them cognitively impaired and unable to care for themselves. Prior to rifaximin, patients had to rely on lactulose – a medication that can cause a range of painful side effects that make life for both patients and caregivers very difficult. Rifaximin has been shown to be very effective in managing HE symptoms and in keeping patients out of the hospital.

Prior to it being approved for use in Canada, many patients have had access to rifaximin via special access programs. Unfortunately, pending CADTH's reimbursement recommendations, some patients are now being denied access and cannot afford to pay for the drug themselves. In one instance, a patient in Newfoundland taking rifaximin had to have her parents cover the \$1,030 monthly cost – an expense they could ill afford as senior citizens on a fixed income.

The Canadian Liver Foundation believes that liver disease patients and their doctors should have access to the most effective treatment options regardless of location and financial status. Rifaximin has a dramatic and life-altering effect on HE patients and their caregivers and can reduce the burden of HE by reducing hospitalizations of patients. Based on its ability to significantly improve quality of life for patients and to reduce the burden on the acute care system, we recommend that rifaximin be made available to all patients who need it without restriction.

Canadian Advocate Network

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Rifaximin (Zaxine)
Name of the patient group	Consumer Advocare Network
Name of the primary contact for this submission:	██████████
Position or title with patient group	██████
Email	██████████████████
Telephone number(s)	██████████
Name of author (if different)	██████
Patient group's contact information: Email	info@optimizinghealth.org
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Address	151 Bloor Street West, Suite 600, Toronto, ON M5S 1S4
Website	www.consumeradvocare.org
Permission is granted to post this submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

1.1 Submitting organization

The Consumer Advocare Network is a registered not-for-profit organization set up in 1999 to provide education and support to patient groups to promote engagement in healthcare policy and decision-making. Advocare provides regular training and produces education materials for use by patient groups and also provides input to health policy makers and healthcare providers. In 2003, Advocare (under the Institute for Optimizing Healthcare umbrella) co-hosted the 2nd Canadian Conference on Hepatitis C. In 2004 and 2005, we collaborated on development and distribution of education and awareness materials on hepatitis B and C. In 2012, Advocare created the Canadian Expert Patients in Health Technology, a network of individuals committed to promoting informed patient engagement at all levels of health policy and decision-making.

1.2 Conflict of interest declarations

Since 2003, the Consumer Advocare Network has received unrestricted educational grants to support education for hepatitis and related conditions from Janssen-Ortho, Roche, Merck, Vertex, and Wyatt Health Management.

██████████ is a volunteer with the Consumer Advocare Network; she is paid by the Canadian Organization for Rare Disorders and the Institute for Optimizing Health Outcomes, both of which also receive unrestricted funding from these entities for other programmes. She has no conflict of interest to declare in the preparation of this submission.

2. Condition and Current Therapy Information

2.1 Information gathering

Information was collected through two sources: individual interviews and a survey posted on Internet. Given that there are a number of groups in Canada supporting patients affected by hepatitis C, the goal here was to focus on those individuals who had experience with rifaximin (Zaxine) or had (recurring) hepatic encephalopathy (HE) and likely candidates for Zaxine. Individuals were recruited for interviews through the liver clinics as well as through patient groups in Canada and the USA. The survey was sent through the Advocare Network to patient groups, with follow up to groups serving patients with hepatitis and/or liver-related conditions.

Individual interviews were conducted with 21 patients and/or caregivers and survey responses were received from 33 others. Among the individual interviews, 62% were patients and the remaining 38% were family member caregivers. Among the survey respondents, two-thirds were patients and one-third were caregivers. We did not include responses from patient or support groups since these views are likely captured by other patient group submissions.

Majority of the patients were between the ages of 40 and 60, with about 10% over 60 and 10% between 30 and 40 years of age. We did not ask about gender, though most of the patients (80%) interviewed were male; conversely, most of the caregivers were female (spouse or child).

2.2 Impact of condition on patients

About two-thirds of the patients interviewed and from the survey had hepatitis C and the remainder had cirrhosis that they believed was not related to hepatitis (alcohol use, drug reaction, or another disease). About 20% of the patients and/or caregivers did not attribute their neurological symptoms to HE; rather, some thought the symptoms were directly related to hepatitis C or cirrhosis.

For most of the respondents, the experience of HE was disorienting and almost totally debilitating. Two themes predominated. The first was the episodic nature of “attacks” that would completely overwhelm them physically and cognitively and often resulting in hospitalization. The second theme was the mental impact, described as “walking around in a fog”, “a constant state of confusion”, “not being there”, and “like my intelligence has gone.” Caregivers spoke of the moodiness, lack of interest in any activities, “sitting around and watching TV all the time”, “withdrawing and not wanting to be social.”

Most patients were unable to continue to work. Only about 10% are currently working and none of those unemployed felt he/she had a chance to return. One respondent, a truck driver, said, “My doctor said I should stop working or else they would take away my license.” Another described the impact as cumulative. “When I have an episode [of HE] I am just sitting around all day getting depressed and stressed, which seems to trigger more bouts of HE.”

Even when patients are not experiencing episodes of acute HE, most have severe symptoms (although some may also be related to the underlying liver condition). We did not question or survey about symptoms not related to HE (not relevant to this drug). Overall, the symptoms that were reported as severe and/or affecting almost all individuals were confusion (including forgetfulness), mood swings, difficulty doing basic cognitive tasks (reading or math), and sluggishness (slowness). Overall, the symptoms that were reported as moderate and/or affecting most people included sleep disturbances

(sleepiness), anxiety (fearfulness), and disorientation (time or place). Finally, respondents reported only mild or infrequent symptoms of slurred speech, shaking, and coma.

Most respondents feel they are unable to manage independently are reliant on family members or other informal caregivers to support daily life management. “I basically have given up trying to count change at the store and just hope they [clerks] are honest.” “I will walk into the room and forget why I was there.” “Sometimes, I can’t figure out where I am or how I got there.”

Another major disruption to the patient and the family are the hospitalizations. “I keep losing my appetite and so I don’t eat enough and then I can’t get rid of the waste. So then I end up in the hospital to get everything flushed out and starting all over again.” “Every time I call the ambulance to go to the hospital, it costs me about 60 bucks. It’s not free, you know.”

2.3 Patients’ experiences with current therapy

We focused exclusively on therapies related to management of HE. In both the interviews and the surveys, we used open-ended questions as well as a list of medications to determine what patients were receiving now, and in the past. All the patients had received and/or were currently receiving lactulose. All were also taking antibiotics; most frequently prescribed was Flagyl (metronidazole), although some were currently using or had previously used neomycin. All of the interviewed patients and caregivers had had access to rifaximin and about 85% of those responding to the survey said they had received rifaximin at least once. The remainder were “not sure.” Only a few (less than 10%) said they were currently receiving Zaxine (presumably through private drug insurance).

Patient reported that lactulose (alone) had worked pretty well in terms of lowering their ammonia levels by increasing their bowel movements (e.g., to three times a day). “I had tried to change my diet and reduce my protein intake, but it wasn’t working. I was constipated most of the time, so I was really pleased when I started the lactulose.” Many reported that it also helped to “clear their head” and “reduce the fogginess.” However, about half also commented on the side effects, including diarrhea, flatulence, stomach cramps, and “feelings of bloating.”

For most patients, however, there was a clear benefit to using rifaximin (in combination with lactulose). Most patients had used rifaximin for six to 18 months, though a few had gotten access only in hospital or immediately after discharge. Most no longer had access to rifaximin after the compassionate use was discontinued (six months or longer). “On rifaximin, I felt my head was clear and I could carry on in a normal way.” “I had a lot more energy and wanted to get out and to be with the family or friends.” “On rifaximin, I did not have to go to the hospital for over six months, and now that it has been taken away, I have been back three times in the last four months. This cannot be cheaper.” One patient indicated that he had been hospitalized while on rifaximin, “but that was probably my fault because I didn’t take it regularly. When I got out, I was much more compliant and had no more hospitalizations.”

Patients also spoke about feeling more “hope” when they were on rifaximin, probably a combination of knowing they were on a therapy that could manage their symptoms but also because they were less confused or anxious.

2.4 Impact on caregivers

What challenges do caregivers face in caring for patients with this condition? What impact do treatments have on the caregivers' daily routine or lifestyle? Are there challenges in dealing with adverse effects related to the current therapy?

Caregivers expressed many of the same challenges as the patients themselves. Interesting, most of the comments were not around the physical care for the person with HE but the emotional toll. They worried about their spouse or parent and their inability to manage independently. "When I am at work, I call my father several times a day and if he doesn't answer, I get very worried and sometimes need to go home to make sure he is okay." "I see how stressed he gets and it makes me very sad." "Our daughters are both grown and not close to home and they worry about their dad all time." "He tends to isolate himself and not want to go out or to see friends; he used to be such a social person, always making others laugh."

Caregivers spoke strongly about the benefits of the patient having access to rifaximin. There were two themes. First, they were happy that their spouse or parent was happier, clearer, "more present" and wanting to take part in activities. "He was more like his old self." Second, they felt less concerned about potential acute episodes of HE that could severely endanger the patient and/or lead to hospitalization. "We didn't have to worry as much, and it was good to just be a family again."

3. Information about the Drug Being Reviewed

3.1 Information gathering

Information in this section came from the same sources as previously described: individual interviews and survey data.

3.2 What are the expectations for the new drug or what experiences have patients had with the new drug?

Most of this information is presented in the previous section since most respondents also had some experience with rifaximin. There are clearly patients for whom lactulose (in combination with antibiotics) is reasonably effective. Most of these patients were not managed well on lactulose and had been prescribed rifaximin because of their unmanaged symptoms and/or hospitalizations. All patients and caregivers expressed their belief that rifaximin would be more effective than lactulose alone, especially in reducing episodes of acute HE and thus reducing the need for hospitalization and fewer days in hospital. In addition, patients and caregivers expected they would experience much better mood, more energy, better sleep, and more interest in participation in daily activities with rifaximin.

"I have not improved on Flagyl at all. The simple things are a chore for me. I feel slower and dumber, and it's scary for me." "The current limitations [without rifaximin] are the wait time in the hospital, the running of tests to see if I have something else. I don't have an immune system so the hospital is a risk by itself."

"I feel more alert." "I think my husband was more hopeful and optimistic on rifaximin."

Patients reported no “additional” adverse effects that could be attributed to rifaximin (and not to the lactulose, as well). Patients expressed the hope that they could experience stable health and well being with rifaximin.

4. Additional Information

When asked how important it was that the drug plans cover rifaximin for patients at risk of recurring HE, about two-thirds said it was “very important” and one-third said “important.” “I can’t understand not providing it when the only other option is hospitalization.” “Right now, it’s like you’re damned with two diseases. I know I still have the liver disease but if I can deal with the HE, it would make a big difference in my life.”

Much of this population relies on the public drug plans. Even from the patients’ perspective, it cannot be less costly to have patients in hospital on a regular basis as a result of acute HE episodes. Certainly, in terms of the patient’s quality of life and for the caregivers, the advantages of Zaxine are significant, even if it does not completely eliminate the need for other medications or “stop HE” in the short term or the long term.

GI (Gastrointestinal) Society

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Zaxine® (rifaximin) for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults
Name of the patient group	GI (Gastrointestinal) Society
Name of the primary contact for this submission:	██████████
Position or title with patient group	██████████
Email	██████████
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Name of author (if different)	
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Address	231-3665 Kingsway, Vancouver, BC V5R 5W2
Website	www.badgut.org
Permission is granted to post this submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

1.1 Submitting Organization

Our mission: As the Canadian leader in providing trusted, evidence-based information on all areas of the gastrointestinal tract, the GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting gastrointestinal and liver health.

Canadian health care professionals request more than 550,000 of our BadGut® Basics patient information pamphlets each year, and tens of thousands of Canadians benefit from our important quarterly publication, the *Inside Tract*® | *Du coeur au ventre*^{MC} newsletter.

Our free BadGut® Lectures from coast to coast cover various digestive and liver conditions for patients, caregivers, and other interested individuals. We also have dynamic websites in English (www.badgut.org) and French (www.mauxdeventre.org). Organized on a number of topics, GI Society support group meetings offer a wealth of information for those newly diagnosed with a gastrointestinal disorder, as well as those who have lived with a condition for years.

Our highly-trained staff and volunteers offer additional patient resources, including responding to information requests and participating in community initiatives. Staff and advisors work closely with health care professionals, other patient groups, governments at all levels, and health care thought leaders on behalf of GI patients. In addition, we occasionally hold continuing education events for pharmacists, nurses, dietitians, and physicians. The GI Society, along with its sister charity, the Canadian Society of Intestinal Research (CSIR – founded in 1976) has supported a number of significant clinical, basic, and epidemiological research projects in the field of gastroenterology.

1.2 Conflict of interest declarations

- a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:
The GI Society receives financial contributions from pharmaceutical companies in support of our independent charitable work for Canadians affected by GI/liver conditions. Supporters have no input into the editorial content of our resource material, which is approved by the GI Society's Medical Advisory Council (made up of GI/liver health experts only). Pharmaceutical companies from whom we have received support of any kind, such as charitable donations or grants, sponsorships, subscriptions to the Inside Tract® newsletter, etc. in the last two years include:

Abbott Laboratories Ltd, AbbVie Corporation, Amgen Canada Inc, Actavis (as Aptalis Pharma, Forest Laboratories, and Warner Chilcott), AstraZeneca Canada Inc., Bristol-Myers Squibb Canada, Canada's Research-Based Pharmaceutical Companies (Rx&D), Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Ltd., Janssen Canada, Merck Canada Inc., Medical Futures Inc., Novartis Pharma Canada Inc., Cubist Pharmaceuticals (as Optimer Pharma), Pfizer Canada Inc., sanofi-aventis Canada Inc., Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc.

- b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:
None. The GI Society has prepared this submission entirely independently of any outside groups or individuals.

2. Condition and Current Therapy Information

2.1 Information gathering

This information was obtained primarily through contact (interviews, etc.) with patients affected by hepatitis C (HCV) and HCV nurse specialists, as well as the expertise of our health care professional council and advisors (gastroenterologists, hepatologists, pharmacists).

2.2 Impact of condition on patients

Hepatitis C (HCV) becomes chronic in approximately 75% of infected people. Most chronic carriers have few or no symptoms but some report fatigue, general weakness, and vague discomfort in the area around the liver. In about 25%, however, chronic HCV can lead to cirrhosis of the liver and cirrhosis may lead to hepatic encephalopathy (HE).

HE affects cognitive functions, causing fatigue, confusion, and forgetfulness. Try to imagine getting through your day when your memory and focus are impeded because your body has to work so hard to clear toxins via a liver whose function is severely undermined by extensive scarring (cirrhosis). The extra complication of HE can eventually lead to seizures, coma, and death.

Hepatitis C (HCV) can affect patients in every facet of their lives, including professional and personal relationships, and in their ability to perform required duties at work and at home. It's one thing to care for one's self, but many with HCV are also caretakers for others.

Many of these patients have said that they are reluctant to disclose their HCV status to family, friends, employers, and other healthcare professionals for fear of rejection, discrimination, or ostracism. HCV

alone can have devastating mental health consequences, affecting a person's ability to maintain personal relationships and to pursue employment goals. Dealing with HE creates an additional, extreme burden on affected patients and they require effective treatment as soon as possible following diagnosis.

Individuals who are physically and mentally healthy are far more productive at home, at their work, and in their communities than those who are not. Healthy people with optimism about their lives and physical health can have a positive impact on reducing the public healthcare burden and lowering healthcare costs.

Improved quality of life from effective HE treatment and prevention from recurrence means individuals are healthier in other ways and, even while battling a chronic disease, are better able to live productive lives.

2.3 Patients' experiences with current therapy

The current standard of care treatment for HE, which often includes taking the laxative lactulose, is helpful for many patients, but it comes with side effects, such as many bowel movements a day, and is not effective alone for many patients. For those for whom lactulose is not effective or does not prevent recurrences of HE, there are no other options.

Affordable access to Zaxine® could be the missing piece of the treatment puzzle that leads some patients – otherwise abandoned to the ravages of repeated episodes of HE - new hope for effective prevention.

2.4 Impact on caregivers

Patients with advanced liver disease and complications like HE are often unable to work or perform major childcare or other caregiver duties. This puts an extra societal burden on other family members. Effective treatment of HE and prevention of recurrences would mean less hardship for the patient and all family members and caregivers.

3. Information about the Drug Being Reviewed

3.1 Information gathering

This information was obtained primarily through contact (interviews, etc.) with patients affected by hepatitis C, hepatitis C nurse specialists, and the expertise of our health care professional council and advisors (gastroenterologists, hepatologists, pharmacists).

3.2 What are the expectations for the new drug or what experiences have patients had with the new drug?

- a) Based on no experience using the drug:
On behalf of the many Canadian patients we represent, the GI Society encourages you to recommend coverage for a crucial new medication that can help more patients suffering from advanced liver disease and the devastating mental health consequences of HE. We understand that two of the most important criteria that CADTH considers are cost effectiveness and the impact a new medication will have on the population. We believe Zaxine® deserves coverage based on both factors.

Studies show that Zaxine® gives health care providers another prevention option for liver disease patients with hepatic encephalopathy when the frontline medication for this condition, lactulose, is not effective (or not effective alone). Not everyone with HE would benefit from Zaxine®, but CADTH should recommend coverage for it for the patients who need it.

While we have not yet had the opportunity to interview patients with HE who have received treatment with Zaxine®, we are aware that many Canadian patients have received successful treatment with Zaxine® over the past few years through the maker's special access program (SAP). While we are thrilled that Health Canada improved this important medication in August 2013, it is now no longer available through the maker's SAP. We believe it is vitally important for these patients that CDATH now recommend this medication for coverage.

Low socioeconomic status is a risk factor for hepatitis C, which means one of the demographics that is most susceptible to becoming affected by HE is also very unlikely to be able to afford this new medication on their own. While they languish with this disease, their chances of recovery are diminished.

We know new medications are expensive, but in the long-term unhealthy people are more of a burden on the health care system than are healthy people. For patients who have severe forms of HCV (e.g., cirrhosis, liver cancer), the long-term effect of being denied appropriate treatment will likely be far more costly, due to liver transplants or other ongoing expensive medical interventions for HE and other complications.

It makes sense to us, and to the patients who we represent, that when a medication is available that prevents further physical and mental suffering related to advanced liver disease, that the individuals who would benefit from it should have reasonable access. Please don't leave hope beyond their grasp.

We urge you to ensure that this Health Canada-approved medication for liver disease patients who have hepatic encephalopathy is included with your list of positive recommendations for coverage.

4. Additional Information

None.

HepCBC Hepatitis C Education and Prevention Society

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	ZAXINE for hepatic encephalopathy (HE)
Name of the patient group	HepCBC Hepatitis C Education and Prevention Society
Name of the primary contact for this submission:	██████████
Position or title with patient group	████████████████████
Email	████████████████████
Telephone number(s)	████████████████████
Name of author (if different)	
Patient group's contact information:	
Email	info@hepcbc.ca
Telephone	250-595-3892
Address	#20-1139 Yates St., Victoria, BC V8V 3N2
Website	www.hepcbc.ca
Permission is granted to post this submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

1.1 Submitting organization

HepCBC is a non-profit society run by and for people infected and affected by hepatitis C. Our mission is to provide education, prevention and support to those living with HCV. Our office with our only paid employee (an office mgr.) is in Victoria, BC. We also have activities and groups in Nanaimo, BC and Surrey, BC. Our representatives attend provincial and federal-level conferences and we give information and support world-wide through our website. We publish a monthly bulletin, the hepcbull. We focus on providing “clean and sober” peer support groups, anti-stigma activities, prevention education to young people, and encourage testing among at-risk groups -- including those who are no longer at risk but may have contracted hepatitis C decades ago. We work alongside local HIV/AIDS organizations in support of co-infected people.

1.2 Conflict of interest declarations

- a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:
 HepCBC Hepatitis C Education & Prevention Society has received funding for hepatitis C-oriented projects such as publishing educational materials, organizing educational forums, attending and presenting at educational conferences, advertising in newspapers (events and hepatitis C patient awareness), and holding awareness activities from the following pharmaceutical companies over the last three years: Merck Pharmaceuticals, Hoffman-LaRoche, Vertex Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb, Boehringer-Ingelheim, and AbbVie.
- b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

The author of this report has attended several educational conferences and meetings for which registration and travel expenses were funded by the pharmaceutical companies listed above.

2. Condition and Current Therapy Information

2.1 Information gathering

This report was developed using data provided by ten (10) individuals:

(1) a patient survey advertised through our website and our email list. In total there were submissions by three (3) patients with hepatic encephalopathy, one of whom is a liver transplant survivor, and two of whom suffer from Primary Biliary Cirrhosis (PBC) and have been taking Zaxine due to for an extended period. One of the PBC patients also has Sjogren's Syndrome.

(2) Input from two (2) HCV+ volunteers who have actively manned HCV+ phone and email support systems for several years, and have extensive knowledge of patient concerns and experiences.

(3) Aggregate input from five (5) HCV+ participants at our August monthly support groups has also been added.

2.2 Impact of condition on patients

As a patient group for those affected by hepatitis C, we at HepCBC have had much experience with people suffering from both minor and major forms of hepatitis encephalopathy (HE). It is indeed a very debilitating condition, even when it manifests in its less severe form, and comes and goes. In the very end stages of liver disease, it is a nightmare for both patients and families. Some of us have watched HCV+ people and their families suffer for years, on and off as HE results in loss of confidence, a job, relationships, and ensuing financial hardship, further agitation, alienation, isolation, anger, and depression. We have also seen people in their last couple weeks of life, first in a state of total agitation and confused, irrational anger at their caregivers, later slipping into a coma. As patients with liver disease, we greatly fear this state, particularly any hurtful things we might say to dear friends, family, and caregivers, especially as this would be their final memory of us. We know that this drug is expensive, and that other less expensive will be – and should be – tried first. But we'd really like to know that ZAXINE is available in our doctors' toolkit if and when the need was there. Not only to prolong our lives, or to add quality time, getting us at least close to normal for however many months or years that this is possible, but also to help ease our final days with friends and family. We present below the actual stories of HE patients, either in their own words, or we give accounts of HCV+ patients we have known. Interestingly enough, only one HCV+ patient (with a liver transplant) sent written input to us through our website, but they are generally eager to share their stories of HE orally.

"I had a liver transplant in April 2002. I was psychotic by this time. I had 7 hemorrhagic bleeds over several years. MRI's demonstrated encephalopathy. For a long time before the transplant large portions of memory were missing. I was argumentative and belligerent. I had 2 car wrecks and don't remember those. I would get lost going home. And couldn't stay in my lane on the freeway... I have peripheral neuropathy and can not to this day hold my balance if I try to walk heel to toe. I have permanent brain damage affecting memory and sleep. I typically sleep 1.5 of 3.0 hours and wake up from REM sleep (a 90 min cycle). Rarely over the last decade have I been able to sleep 4 hours. I had an Extensive Neuropsychiatric Evaluation after the transplant and the diagnosis was cognitive impairment. Due to slow processing speed. Because of multiple

procedures and surgeries I have a very high tolerance to sedatives. I nap up to 4 times a day to catch up on sleep. I often fall asleep spontaneously (in recliner & movie theaters. If my mind is a little cloudy I do not drive...(example of how bad sleep patterns are):...I took 10 x 10mg Valium recently to no effect, after trying 2, then 4, then 5. .Then I mixed 20 mg Valium & 20 mg Ambien and slept for 6 hours. What a relief. The next night that dose had no effect and I doubled it after waking up at 3:00AM. Nothing works.”

“I have Primary Biliary Cirrhosis and Sjogren’s Syndrome. My more severe symptoms include shaking of hands or arms, agitation, excitement, disorientation. drowsiness and confusion, slowed or sluggish movement, and problems concentrating. In short I have problems functioning well in my day-to-day life. Every activity in my life is affected. Fatigue prevents many activities.”

2.3 Patients’ experiences with current therapy

(liver transplant HE sufferer): “All I had was LACTULOSE which I absolutely hated the sweet syrupy taste. I had to stay near a toilet-because it would act 0-4 hours after taking. I eventually had to take it because I could not hold my balance or walk straight.”

(PBC HE sufferer): “In 2007 I was diagnosed with Primary Biliary Cirrhosis. My hepatologist prescribed URSODIOL. At that time I was virtually symptom free and remained that way until 2011 when my first attack of HE occurred. It was characterised by disorientation, loss of coordination, slurred speech, stumbling gait, and inability to focus mentally. Because of this [NOTE: unusual for PBC] presentation, it was felt by my doctor that I had had a slight stroke. However, in consultation with the stroke clinic it became clear that that was not the case. The symptoms lessened but never really disappeared but nobody really knew what to do with me. I went to Emergency three or four times but there was never a conclusive diagnosis. One doctor prescribed LACTULOSE but, since I didn't really understand its purpose I was inconsistent about taking it. I continued in this foggy state for over a year. The attacks occurred several times. I was prescribed CIPROFLOXACIN; it was somewhat helpful for a short time but soon had no effect in the long term. Fifteen months after my first HE attack, I had an extremely serious attack. Not only did I demonstrate the earlier mentioned symptoms but in addition I was delirious and behaving in a totally uncontrolled manner. To this day, I have absolutely no recollection of those two days.”

“When I was released from the hospital, I went to see my hepatologist. As it happened, he was able to get access to RIFAXIMIN through a special access program.”

(Patient with PBC and Sjogren’s Syndrome): “For several years, I have taken both ZAXINE (through Compassionate Study program of Salix) and LACTULOSE. LACTULOSE causes loose stools and for that reason I use it seldom.”

(HCV+ patient who works as a volunteer at HepCBC): “I have known six patients with severe HE, and all lost their jobs and became alienated from their families during their periods of HE. Two eventually got liver transplants and are doing great now. One is still awaiting a transplant and though he is out of a hepatic coma at present, he is dealing with HE and related depression daily. Two almost died and are still quite ill, but have overcome most of their HE, enough to do volunteer work but not to hold down a paying job. The last died a terrible death over a very

short time. All of these six patients took LACTULOSE alone for their HE and other symptoms of ESLD; no other drugs were used.”

“LACTULOSE helped keep the first three alive while awaiting a liver, though they were slipping in and out of coma. The two who now volunteer are still taking LACTULOSE regularly, and it helps them maintain their mental strength. Perhaps if ZAXINE were available to them, they would be able to hold down a paying job and support their families. Doctors could at least try ZAXINE with patients such as those if it were covered by Pharmacare. The patient who died did not respond at all to LACTULOSE, and died of an intestinal obstruction. If she had been able to take ZAXINE, she might be alive today.”

2.4 Impact on caregivers

(PBC patient): “...Although I am the one with the disease, my husband was extremely effected also. I needed careful watching, I was never left alone for any extended time, and all my actions were monitored. Since a lot of my bizarre behaviour occurred at night, he always slept lightly so that he could hear me if I was out of bed.”

(Partner of patient with PBC and Sjorgren’s Syndrome): “Since patient began taking ZAXINE the impact of her condition on my life has been considerably less. Less worry because patient is more energetic, mood is more optimistic. Concentration and focus is better. Fatigue improved. Able to eat foods containing protein again. Able to gain some weight , now back to normal. Looks good too. Definitely less fatigue. Better daily function. ZAXINE works beyond our expectations to help clear up HE symptoms.”

3. Information about the Drug Being Reviewed

3.1 Information gathering

Same as in Section 2.1.

3.2 What are the expectations for the new drug or what experiences have patients had with the new drug?

- a) Based on no experience using the drug:
- Lives of patients would be greater in both length and quality.
 - This drug is great for those people who cannot take LACTULOSE, or who experience a better result when it is added to their LACTULOSE regimen.
 - While we have not heard specifically that patients would put up with side-effects of this drug in return for its benefits, we have heard no reports of side-effects from it.
 - This drug would likely result in fewer deaths, fewer coma patients, more successful transplants, fewer hospital visits, less time off work, greater financial stability, greater mental stability, and fewer family breakdowns.
- b) Based on patients’ experiences with the new drug as part of a clinical trial or through a manufacturer’s compassionate supply:
- (PBC patient) “...When I was released from the hospital, I went to see my hepatologist. As it happened, he was able to get access to RIFAMIXIN through a special access program [SAP through US manufacturer, Salix] .This drug gave me a new life! I could actually feel the fogginess dissipate. I can focus, multi-task and problem solve, all the cognitive abilities one expects to have. My coordination has returned. I still have some trouble remembering events and

physically I have very limited stamina but I have come such a long way all as a result of RIFAXIMIN.”

(Patient with PBC and Sjorgren’s Syndrome): “Good. Can function better. Improved Feeling of well being. I have been on the study for ZAXINE and I have been on the drug for a few years. Made my Life livable. Have been using ZAXINE for a few years. Improves my wellbeing and health. No side effects! I can live again.”

“Positive effects on my symptoms (shaking of hands or arms, agitation, excitement, disorientation, drowsiness or confusion, slowed or sluggish movement, and problems concentrating. The best result is it allows me better concentration. I am able to focus better with less Confusion and improvement in Calmness.”

“There are no adverse events or Negative Effects. And it sure is easier to use than the other drugs. More convenient. Less unpleasant.”

“Now with taking ZAXINE, I can live a good life with dignity.”

“When the Study concluded; there was no access to ZAXINE in Canada. I contacted [representatives’ names] from Salix, USA. They have been wonderful and have been providing me with ZAXINE on a compassionate level. I am grateful to [representatives’ names] from Salix USA for allowing me to have a better quality of life!”

“Unfortunately ZAXINE is Out of Reach expensive, \$1400 to \$1600 a month so (without reimbursement by Pharmacare) is not accessible as of yet to the public.”

4. Additional Information

(PBC patient): “I hope this account is helpful to you. I can't imagine what state I would be in without this medication.”

(Patient with PBC and Sjorgren’s Syndrome): “I know that ZAXINE could help a lot of people with this condition to have a better quality of life. I believe many people have this condition, but they have not been diagnosed yet. ZAXINE must become readily available and affordable to All Canadians.”

(HepCBC): We fully support listing ZAXINE in Canada for use with any patient with HE, either added to other drugs such as LACTULOSE, or as a stand-alone, depending on the patient’s needs. We recognize the cost factor would likely not make it the first drug to try, but to have it available (and financially accessible) to deal with this terrible condition would be a real blessing to these patients and their loved ones.