



## Common Drug Review *Patient Group Input Submissions*

### **Glycerol phenylbutyrate (Ravicti) for urea cycle disorders**

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

Canadian Organization for Rare Disorders — permission granted to post.

#### **CADTH received patient group input for this review on or before September 21, 2016.**

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 Organization for Rare Disorders

### Section 1 — General Information

<b>Name of the drug CADTH is reviewing and indication(s) of interest</b>	Ravicti (Glycerol phenylbutyrate)
<b>Name of the patient group</b>	Canadian Organization for Rare Disorders
<b>Name of the primary contact for this submission:</b>	[REDACTED]
Position or title with patient group	[REDACTED]
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#### 1.1 Submitting Organization

The Canadian Organization for Rare Disorder (CORD) is Canada's national network for organizations representing all those with rare disorders. CORD provides training and support to patient organizations serving rare diseases. In the situations where there is no existing patient group, CORD has served as the voice for those patients, including preparation of submissions for drug review processes or other activities on behalf of the patients and families.

#### 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 Canadian Organization for Rare Disorders receives funding from several pharmaceutical companies, including Horizon, the manufacturer of Ravicti but also from Medunik Canada (provider of Pheburane), and others: Abbvie Canada, Actelion Pharmaceuticals, Aegerion Pharmaceuticals, Alexion Pharmaceuticals, Amgen Canada, Amicus Therapeutics Inc., ApoPharma, Bayer, Bayshore Home Health, BioMarin Pharmaceutical, BIOTEC Canada, Canada's Research-Based Pharmaceutical Companies, Celgene, CSL Behring Canada, Genzyme Canada, Gilead Sciences Canada, GlaxoSmithKline, Hoffman-LaRoche, Ikaria, Innomar Strategies, Mark Krueger & Associates, Merck Frosst Canada, NPS Pharma, Novartis Pharmaceuticals Canada, Pfizer Canada, PTC Therapeutics, Rare Disease Therapeutics, Sanofi Canada, SHIRE Human Genetic Therapies, Sigma-Tau Pharmaceuticals Inc., Valeo Pharmaceuticals Inc, and Vertex.

b) *We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:*

Durhane Wong-Rieger is the paid President of COD. There is no other conflict of interest.

## Section 2 — Condition and Current Therapy Information

### 2.1 Information Gathering

Information was collected through several venues, including one-on-one interviews with patients and parents, leads of patient advocacy groups in the USA, healthcare professionals who were referring patients and parents, and Internet survey (Survey Monkey) promoted by healthcare professionals, websites, Facebook groups (public and private), blogs, and emails. Patients and parents in the USA and Canada were contacted (see response in Section 3).

### 2.2 Impact of Condition on Patients

Urea cycle disorder is a genetic condition but onset and severity are characterized as “highly variable” depending on the specific genetic mutation and other factors. Onset of symptoms may vary from birth to childhood to adulthood. Except for those diagnosed at birth, almost all of patients reported suffering for a period of time, sometimes years, before getting an accurate diagnosis. More than four-fifths of those responding were diagnosed as children, with almost 1 in 5 diagnosed at or near birth (under 2 months). About 80% have been living with a UCD diagnosis for more than five years. Almost one-half had experienced symptoms for less than one year prior to diagnosis, but about one-fourth had been symptomatic for up to two years, and one-fourth for up to five years. “My mom knew there was something wrong, but they kept telling her she was crazy.”

Symptoms rated as causing “much or very much” impact by two-thirds of respondents were abdominal related, including cramps, pain, diarrhea, vomiting, and eating disorders. Similarly, almost everyone reported the experience of fatigue, lethargy or weakness, with more than half rating these symptoms as causing “much or very much” impact. In addition, 30% said hospitalizations had affected them “much or very much”; serious medical conditions (liver complications or coma) had affected fewer (20%).

Almost one-third (30%) said the UCD was related to serious behavioural problems, while another 50% said there was some impact. The percentage reported serious learning or cognitive disorders was similar (20% reporting the effect as “much or very much” and 50% said “some” impact). More than one-third (35%) rated the impact on school or work life as “much or very much”; and the same percentage reported serious impact on home and/or social life.

But these statistics do not adequately convey the impact of the challenges of living with UCD. The words of the patients are very informative. One adult patient, diagnosed as a child, said, *“I missed many school days due to being in the hospital; when I returned I was constantly behind and felt like a failure. As I grew older it started to effect [sic] the ability for me to keep a job due to doctor appointments, hospitalizations, lack of energy. It has caused severe anxiety at times not knowing when the next flair up may be. It has affected my ability to remember things at times. It is an ongoing struggle and I hope they find a cure. My veins are completely gone more or less. I have had IV all over since so many hospital stays.”*

For respondents with adult-onset symptoms, the impact can be overwhelming. *“Urea Cycle Disorder has not affected my life--it IS my life. ...I follow a protein-restricted diet and I take care of myself...but I always live in fear of when the next virus, the next stressor, the next metabolic change could make my ammonia skyrocket and put my life in danger.”*

*“I didn’t realize I had this condition until later in life; I had never liked meat and had practiced food avoidance. I also remember being sick a lot as a kid, stomach aches and vomiting. I had 3 babies who were totally fine. My 4th baby started getting sick when he was born; before he could be diagnosed, at 3 days old, he passed away. Following the autopsy, they asked about my diet, and they told me my son passed away from UCD.”*

### 2.3 Patients’ Experiences With Current Therapy

All of the participants reported being on primary drug treatments to remove ammonia from the bloodstream. Nearly four-fifths had taken sodium benzoate/sodium phenylacetate (Ammonul) in the past, and about 8% reported taking it at the time of responding. Only 15% said they had never taken the drug. About 80% had taken sodium phenylbutyrate powder or pills (Buphenyl) but the remaining one-fifth had no experience with this drug. In terms of newer drugs, about 8% were taking sodium phenylbutyrate granules (Pheburane) and 75% were currently taking glycerol phenylbutyrate (Ravicti) and 12% had taken it in the past. About one-quarter reported also taking arginine HCL (Citruline).

For patients who had been diagnosed prior to availability of NaPB, the introduction of Buphenyl was considered to be a significant improvement on previous medication and diet alone. Adults reported being able to significantly improve their ammonia levels if they were highly compliant with their diet and drug treatment.

*“Sodium benzoate just wasn’t enough. So when Buphenyl came along, I was really committed to taking the medicine. I know a lot of people complain about the smell, the taste, and the number of pills you have to take, but I’m obsessive by nature, so it worked for me.”*

Said one parent about their lives prior to Buphenyl, *“Until she was 13, I would check her all night long, and some nights I knew something was wrong; I would just grab her and take her to the hospital”*

*“When [my son] was diagnosed [at age 12], we started sodium phenylbutyrate powder, which meant mixing it three times a day; it had a strong taste, was hard to mask and mix, and he had a hard time taking it. With the pills, he was taking 18 of them daily but I could only be sure he was taking them at breakfast and after school.”*

*“[With] Buphenyl, sodium benzoate, and Citrulline-L have kept my daughter's ammonia relatively controlled for about 6 years.”*

But all patients acknowledged that sodium phenylbutyrate was far from an ideal treatment. A major limitation to effectiveness is compliance. *“When [she] was little, we tried mixing the powder into a smoothie or puddings or anything to mask the odour and the taste, but she would still gag and throw half of it up. We couldn’t send it with her to school (it didn’t come in a labeled bottle and they wouldn’t mix the ingredients there) so she was always missing one dosage a day.”*

*“NaPB ruled our lives; [our daughter] wouldn’t do sleepovers; on vacation, we always had to eat in our hotel room because she was afraid of throwing up in public.”*

*“Buphenyl saved my life...but ended up harming me as well. It caused my blood pressure to rise to quite dangerous levels. And it tasted horrendous and was so very difficult to swallow...especially when you need to take 50 pills of it a day like I did. Yes...50!”*

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*“My 13-year-old daughter has been on NaPB since 2 years old. It is very harsh and she was taking 30 pills a day. It irritates her throat and she gets ulcers. We had to home school her until 7 or 8 years old.”*

*“Taste is a huge issue. Not fun having to give this med to a baby.”*

For adolescents and adults, the odour related to the medicine had a serious impact. One parent reported, *“The medication has a terrible smell that comes out in the sweat glands. Their clothes and sheets would take on the same sickly smell that made life difficult in school and with friends.”*

Another issue was that ammonia levels were not sustained at consistent levels on Buphenyl.

*“The absorption rate was also inconsistent causing her ammonia levels to have distinct peaks and valleys, rarely level.”*

*“Between 7 pm and 8 am, her levels were unstable; sometimes, she was so groggy, it was hard to get her up in the morning.”*

*“When you have an infection or the flu, it is hard to take 50 pills, so then your ammonia levels will be affected.”*

While some patients felt that Pheburane was a better alternative to Buphenyl, others were not as positive. About 60% of patients on Buphenyl reported stomachaches, cramps, and diarrhea and those on Pheburane reported similar issues. *“It is still the same formulation as Buphenyl, so shouldn't be surprising that it causes the same problems.”*

All patients taking Pheburane reported some “difficulty taking the medication.” One parent noted that the capsules sometimes get stuck in their children’s teeth; another reported that the children couldn’t swallow quickly enough, so the coating comes off in the mouth, and the remaining drug causes a “more negative experience” than the NaPB liquid. Moreover, patients with a GI line for Buphenyl cannot use it with Pheburane because of the coating.

One respondent noted that the liquid formulation of Pheburane was not convenient. It has a shelf life of only 14 days, which means it must be shipped out every two days, which is “just not practical.” Also, because the volume of medication is about the same as Buphenyl liquid, babies and small children experience the same challenges leading to nausea and vomiting. For adults, the required dosage is the equivalent of a bottle of Pheburane every 1.5 days, which means getting 30 to 45 bottles shipped every month. *“I don't know what genius thought this was a good idea. At least with Buphenyl, the liquid can be dispensed as a 500 ml to 1000 ml bottle that is stable for 30 days.”*

*One parent of a 17-year-old said, “My son is starting community college this fall. He is currently on Pheburane but we were hoping to have Ravicti before he left home since it would be so much easier for him to manage. The Pheburane is not portable since it is such a big bottle. I know Ravicti has been approved so I don't understand why they'll pay for the Pheburane and not the Ravicti.”*

### 2.4 Impact on Caregivers

Parents spoke of caring for a child with UCD as a “full-time” job and some have been providing intensive care from infancy. Most expect that they will be caring for their “adult” child for the rest of their lives.

*“At age 1 ½, my daughter couldn't walk and was slow in other things; she had bouts of vomiting and severe diarrhea but every time we were at the doctor's, she was having a ‘good day’ until we took her to a dietician on a “bad day” when she was throwing up everything. The dietician immediately called a*

neurologist who ran some tests but couldn't find anything. She was down to 15 pounds so they kept her in hospital for two weeks and "force fed" her with regular food; three days after we got home, she slipped into a coma. Her ammonia level was over 700. They diagnosed UCD, flushed out her system, and prescribed medication, rest, and diet.

*In the words of another parent, "It has changed every part of my life and my daughter's! She was in and out of the hospital about every 3 weeks. She lost her speech and ability to walk because of brain damage from the high ammonia and so much time in hospital. I do not work because UCD is a full time job; it was too much for her father and we got a divorce and my mom has moved in with me to help so I can have some respite care."*

*"My daughter ... now 15 years old... has been hospitalized 40 times due to the disorder. She has a feeding tube. She has to be on a special low protein diet."*

*"At age 15, [my son] went into a coma and they said it was the flu and just sent him home. A couple months later, he almost didn't come out of a second coma, and that's when they diagnosed UCD. [His] social life is much different now. He has experienced bullying and has been shunned by his friends. He used to be very sports oriented, and now he is being told to stop playing hockey. After having a normal life, it is difficult to deal with the fact that he no longer will live the life that he once has known. As for me, [m]y day consists of stress...and people just don't seem to understand what we go through!"*

*"Almost every holiday, party and other milestones in your life involve food - birthdays, weddings, etc. It is difficult trying to find substitutions that don't make your child feel different in these situations. Taking medication that is horrible tasting and hard to take doesn't make that any easier."*

## Section 3 — Information about the Drug Being Reviewed

### 3.1 Information Gathering

There is no patient group in Canada for Urea Cycle Disorder (UCD) but there are patients are treated at specialized metabolic clinics. We gathered information from a couple of USA-based groups for patients and research, National Urea Cycle Disorders Foundation and Urea Cycle Disorders Consortium. To collect information directly for this submission, we reached out to two Facebook groups: UCD Survivors and UCD Awareness. We spoke with group leaders and joined the UCD Survivors Facebook where we recruited participants to be interviewed and also to complete our survey (available on Survey Monkey).

Overall, we obtained direct feedback from 52 families (patients and parents). We conducted 18 individual telephone interviews; 10 were parents, six were patients, and two were both. Twelve families lived in the USA and six in Canada. Ten of these also completed the survey, so there were 44 survey respondents. We identified those who also had responded to both survey and interviews so as not to count their feedback twice. We also spoke with six healthcare providers, including clinicians, nurses, and dietitians to obtain contextual information and to seek referrals to patients.

### 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:*

About 90% of the respondents said they had some or much knowledge about Ravicti. For patients who have been on Buphenyl, the expectations are improvement in symptoms, fewer side effects, better quality of life, and improved compliance. As stated by one patient, "[Ravicti will] ... stabilize ammonia levels, restore energy, eliminate or reduce cramps and diarrhea, allow return to normal activities and support compliance because it is easy to take."

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Patients said Ravicti will be better tolerated, and that will lead to improved compliance and that, in turn, will result in more stable ammonia levels. *“From everything we’ve heard, Ravicti is very manageable. It is easy on the stomach and it regulates ammonia levels better than Pheburane. It is more portable, and you can “cheat” with it a bit, so you don’t have to worry about your child as much.”*

*“No bad odour makes life easier. Relationships are no longer as difficult because you are not always worried about how you may be smelling if you are exerting yourself.”*

As detailed in Section 2.3, many of those currently on Pheburane are also hoping for access to Ravicti as soon as possible, citing hopes for increased effectiveness, tolerance, and ease of use.

b) *Based on patients’ experiences with the new drug as part of a clinical trial or through a manufacturer’s compassionate supply:*

About three-fourths of the respondents report having taken Ravicti, either currently or in the past. For patients and parents, the overwhelming response is positive. With Ravicti, patients report a more stable ammonia level, without the “peaks and valleys”, which reduces anxiety and fear, especially overnight.

*“When I say Ravicti is life-changing, I mean completely!” “I know my daughter is getting her dosage three times daily; they can administer the second dosage right at school.”*

*“With Buphenyl, we were still rushing to the hospital several times a year and since Ravicti, she has been hospitalized only three times in six years.”*

*“Previously, my daughter had stopped doing any of her activities because of pain and fatigue with the Buphenyl. Since Ravicti, she is back doing everything and enjoying life.”*

*“Buphenyl left a bad taste ... caused her not to want to eat. This caused her to get catabolic which made it even harder to control her ammonia. The absorption rate was also inconsistent. Ravicti ... corrected all of these issues and has been a miracle for her.”*

*“My daughter is 4 now and has been on it since she was two but when her levels are good she is much less agitated and she seems to be much more clear mentally.”*

*“No bad odour makes life easier. Relationships are no longer as difficult because you are not always worried about how you may be smelling if you are exerting yourself.”*

About 12% had received Ravicti as part of a trial but no longer had access. *“I had resisted going on the clinical trials because I knew that if this was as good as anticipated, it would be very difficult to go back [to our previous drug.]”* This situation was especially difficult for parents. *“Life was so much better with Ravicti. I can only hope that it will be available soon.”*

In terms of adverse effects, most patients reported almost no side effects. Of those experienced, most frequently mentioned were stomach cramps, nausea, diarrhea, headaches, swelling, vomiting, and anemia. All respondents said that the symptoms reduced over time or were manageable with other strategies, such as eating with the medication. No one had discontinued Ravicti.

## Section 4 — Additional Information

The following comments from patients and parents sum up the feelings of the community.

From one patient, *“It's a hard disorder to live with. Even with the Ravicti you have to take a lot of other medication. With Ravicti it makes your whole life a lot easier!!!”*

From a USA parent, *“Pass it on Canada, give people with UCD's the chance to have a life.”*

**Plea to provider and payer, “There are so many benefits that everyone should have access to it!! I wish that.**