Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

danicopan (Voydeya)

(Alexion Pharma GmbH)

Indication:

As an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have residual hemolytic anemia due to extravascular hemolysis (EVH).

April 15, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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Patient Input

Name of Drug: Danicopan

Indication: Paroxysmal Nocturnal Hemoglobinuria

Name of Patient Group: The Canadian Association of PNH Patients & Aplastic Anemia

Author of Submission: Barry Katsof & Cindy Anthony

1. About Your Patient Group

The Canadian Association of PNH Patients

Established in 2009, this patient advocacy group is a non-profit Canadian organization dedicated to serving individuals affected by Paroxysmal Nocturnal Hemoglobinuria (PNH). Its mission is twofold: to connect Canadians impacted by PNH and to advocate for optimal patient care, ensuring access to the latest tools and information for managing the condition effectively. Additionally, the organization offers support to caregivers and endeavors to raise awareness and understanding of PNH.

The Canadian Association of PNH Patients was initiated by Barry Katsof, a PNH patient, driven by his recognition of the inadequate support available to individuals in need of life-sustaining medications. Barry's own journey, characterized by successful self-advocacy in accessing the first biologic treatment, inspired him to extend his knowledge and support to all Canadians affected by PNH. Today, he channels his experiences to assist every Canadian PNH patient facing similar challenges to those he encountered back in 2007. The website is: http://www.pnhca.org

Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)

AAMAC was established in 1987 by a parent deeply affected by their child's aplastic anemia diagnosis. Among its primary objectives was advocating for the creation of a national bone marrow donor registry in Canada. Today, AAMAC stands as a federally incorporated and registered national charity with a bold mission: to offer comprehensive support to every Canadian affected by aplastic anemia, myelodysplasia, or PNH, including patients, family members, friends, and healthcare providers. The website: https://aamac.ca/

About PNH

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disorder of the hematopoietic stem cells, characterized by the abnormal proliferation of red blood cells (RBCs) that lack certain proteins, notably CD55 and CD591. These proteins play a crucial role in protecting RBCs from destruction by the body's immune system. In PNH, the deficiency of these proteins renders RBCs susceptible to complement-mediated destruction, leading to episodes of hemolysis, particularly at night.

The hallmark clinical features of PNH include hemolytic anemia, thrombosis, and bone marrow failure2. Patients often present with symptoms such as fatigue, shortness of breath, dark urine (due to hemoglobinuria), abdominal pain, and dysphagia. Thrombosis is a significant concern in PNH, as it can lead to potentially life-threatening complications such as stroke, myocardial infarction, and pulmonary embolism.

The diagnosis of PNH typically involves a combination of clinical evaluation, laboratory tests, and flow cytometry to detect the absence of CD55 and CD59 on the surface of RBCs and other blood cells[3]. High-sensitivity flow cytometry has become the gold standard for diagnosing PNH due to its ability to detect small populations of PNH cells.

Management of PNH aims to control symptoms, prevent complications such as thrombosis, and improve quality of life[4]. Treatment options include supportive measures such as blood transfusions to manage anemia, as well as targeted therapies to reduce

hemolysis and prevent thrombosis. Eculizumab, a monoclonal antibody that blocks the complement cascade, has revolutionized the management of PNH and significantly improved outcomes for patients.

In recent years, research in PNH has focused on understanding the underlying pathophysiology of the disease, identifying novel therapeutic targets, and developing new treatment modalities[5]. Emerging therapies, including complement inhibitors with improved pharmacokinetic profiles and novel agents targeting the underlying molecular defects in PNH, hold promise for further advancing the management of this complex disorder.

About Extravascular hemolysis (EVH)

Extravascular hemolysis is a process where red blood cells are destroyed outside of the bloodstream, typically occurring in the spleen and liver. In conditions like Paroxysmal Nocturnal Hemoglobinuria (PNH), extravascular hemolysis is a significant contributor to the symptoms and complications experienced by patients.

Here's a deeper look into how extravascular hemolysis impacts patients' lives:

- Symptoms: The destruction of red blood cells outside of the bloodstream leads to the release of hemoglobin, which can cause symptoms such as fatigue, weakness, and shortness of breath. These symptoms can significantly impair a patient's ability to carry out daily activities, affecting work, social life, and hobbies[3].
- Anemia: Extravascular hemolysis contributes to the development of anemia, a condition characterized by low levels of red blood cells. Anemia can exacerbate symptoms like fatigue and weakness, further impacting a patient's quality of life[5].
- Iron Overload: As red blood cells are destroyed, the body releases iron from hemoglobin. Over time, this can lead to iron overload, which can cause complications such as organ damage and increased risk of infections. Managing iron overload through treatments like iron chelation therapy becomes essential in mitigating its impact on patients' health[3].
- Impact on Organs: Chronic extravascular hemolysis can lead to the enlargement of the spleen and liver, as these organs work to clear the damaged red blood cells. Enlargement of these organs can cause discomfort, abdominal pain, and complications such as portal hypertension[4].
- Quality of Life: The chronic nature of extravascular hemolysis and its associated symptoms can have a profound impact on patients' quality of life. Fatigue, weakness, and other symptoms can limit physical activity, social interactions, and overall well-being. The unpredictability of symptom flare-ups can also lead to anxiety and stress[4].

Managing extravascular hemolysis in conditions like PNH often involves a combination of treatments aimed at reducing hemolysis, managing symptoms, and preventing complications. These treatments may include targeted therapies like Danicopan. Additionally, providing patients with education, support, and resources to cope with the impact of hemolysis on their daily lives is crucial for holistic care.

2. Information Gathering

Unfortunately, the Canadian clinical trial for Danicopan had a limited enrollment size, allowing us to gather personal experiences from only one Canadian patient receiving this treatment. As a result, our submission will primarily focus on illustrating the findings of the study and highlighting the potential efficacy of Danicopan in addressing extravascular hemolysis in adult patients diagnosed with PNH. While the sample size may have be small, and the duration of the clinical trial may have been short the insights gained from this one patient's perspective provide valuable firsthand information that contributes to our understanding of Danicopan's impact and benefits for individuals living with PNH in the Canadian context.

3. Disease Experience

Paroxysmal nocturnal hemoglobinuria (PNH) can have a profound impact on patients' and caregivers' day-to-day lives and overall quality of life. Here are some ways in which the disease affects them:

1. Fatigue and Weakness: Chronic anemia due to hemolysis leads to persistent fatigue and weakness, making it challenging for patients to engage in daily activities or maintain employment. This fatigue can significantly impact their quality of life and ability to perform routine tasks[6].
2. Symptom Management: Patients often experience a range of symptoms such as abdominal pain, dysphagia, shortness of breath, and dark urine due to hemoglobinuria. Managing these symptoms requires ongoing medical attention and may involve medication management, dietary adjustments, and lifestyle modifications[7].
3. Psychological Impact: Living with a chronic and potentially life-threatening condition like PNH can take a toll on patients' mental health. They may experience anxiety, depression, or feelings of uncertainty about their future, leading to decreased quality of life and overall well-being[8].
4. Treatment Burden: The need for regular medical appointments, laboratory tests, and treatments such as blood transfusions or targeted therapies like Eculizumab can be burdensome for patients and caregivers. Treatment schedules may disrupt daily routines and require significant time and resources to manage[9].
5. Financial Strain: The cost of PNH treatment, including medications, medical appointments, and supportive care, can place a financial burden on patients and their families. This financial strain may impact their ability to afford essential expenses and contribute to overall stress and anxiety[10].

Understanding the multifaceted impact of PNH on patients' and caregivers' daily lives is crucial for providing comprehensive care and support. Beyond the physical symptoms and medical interventions associated with this rare hematologic disorder, PNH can profoundly affect various aspects of individuals' well-being and quality of life. Here are additional insights into how PNH influences the day-to-day experiences and overall quality of life for patients and caregivers, shedding light on the challenges they face and the importance of holistic management approaches.

1. Social Isolation: Due to fatigue, unpredictable symptoms, and the need for frequent medical appointments, patients with PNH may experience social isolation. They may miss out on social gatherings, family events, and other activities, leading to feelings of loneliness and disconnection from their support networks[11].
2. Work and Productivity: PNH can significantly impact patients' ability to work and maintain employment. Fatigue, symptoms such as abdominal pain and dysphagia, and the need for medical appointments may interfere with job performance, leading to absenteeism and reduced productivity. This can have financial implications and affect patients' sense of fulfillment and purpose[12].
3. Physical Limitations: Some patients may experience physical limitations due to symptoms such as dysphagia, which can affect their ability to eat and drink normally. This may require dietary modifications, such as consuming softer foods or liquids, and can impact patients' enjoyment of meals and social interactions involving food[13].
4. Emotional Well-being of Caregivers: Caregivers of patients with PNH also experience significant emotional and psychological burden. They may worry about their loved one's health, manage caregiving responsibilities, and cope with their own feelings of stress, anxiety, and uncertainty about the future. Providing emotional support and practical assistance to patients can be demanding and may lead to caregiver burnout if not adequately addressed[14].
5. Impact on Family Dynamics: PNH can affect family dynamics and relationships, as caregiving responsibilities and medical needs may become a central focus within the family. Siblings, children, and other family members may need to adjust their roles and routines to accommodate the needs of the patient with PNH, which can lead to changes in family dynamics and communication patterns[15].
6. Treatment Side Effects: While treatments such as Eculizumab and Ravulizumab can effectively manage PNH symptoms and improve quality of life, they may also be associated with side effects or complications. Patients may experience infusion reactions, infections, or other adverse effects that require additional medical attention and monitoring[16].

For caregivers, supporting someone with PNH can also be demanding. They may need to assist with daily tasks, provide emotional support during symptom flare-ups, and coordinate medical appointments and treatments. This can place a significant burden on their own physical and emotional well-being. Quality of life for both patients and caregivers can be greatly affected by the unpredictability of PNH symptoms and the need for ongoing management. The fear of complications such as blood clots and organ damage further add to the stress and anxiety associated with the illness.

In terms of controlling aspects of the illness, managing hemolysis and preventing thrombosis are critical treatment goals in PNH. Hemolysis not only leads to anemia and fatigue but also contributes to other complications such as thrombosis, which can have severe consequences. Therefore, therapies that target hemolysis, such as Eculizumab and emerging treatments like Danicopan, play a crucial role in improving patients' quality of life and reducing disease burden. Additionally, addressing symptoms such as abdominal pain and dysphagia can also significantly impact patients' day-to-day functioning and overall well-being. Overall, a comprehensive approach to managing PNH that addresses both symptom control and disease progression is essential for optimizing patients' outcomes and quality of life.

4. Experiences With Currently Available Treatments

The complement system plays a crucial role in the immune response, but when dysregulated, it can contribute to various diseases, including PNH. Currently available treatments for PNH include C5 inhibitors such as Eculizumab (Soliris), Ravulizumab (Ultomiris) and C3 inhibitor, Pegcetacoplan (Empavali). The C5 and C3 have revolutionized PNH management by effectively inhibiting membrane attack complex formation, thereby preventing intravascular hemolysis (IVH), thrombosis and EVH. Soliris has demonstrated patient survival rates comparable to the general population over a 20-year follow-up in real-world settings, while Ultomiris, where available, has become the standard of care for PNH, with an impressive overall survival rate of 98.4% at 6 years for treated patients[17]. Pegcetacoplan became the third Health Canada-approved treatment for adults with PNH, and the first treatment to target C3, a complement component upstream of C5.

Despite the C5 advancements, approximately 20% +/- of PNH patients continue to experience EVH while on Ultomiris or Soliris therapy; many patients continue to exhibit persistent anemia (manifested as fatigue/extreme fatigue) and require frequent blood transfusions. The patient we interviewed has experienced a near life-threathening anemia. This highlights the need for add-on therapies to address residual hemolysis and further optimize patient outcomes when on the current C5 approved inhibitor. The efficacy and safety of Danicopan, an oral factor D inhibitor, as an add-on treatment to Ultomiris or Soliris in PNH patients with EVH, was evaluated in a phase 3, randomized, double-blind, placebo-controlled superiority clinical trial. Danicopan is the first oral complement inhibitor treatment demonstrating efficacy and safety in PNH patients as an add-on therapy.

Previously reported 12-week data from the double-blind treatment period demonstrated the superiority of Danicopan over placebo on primary and key secondary endpoints[18]. This included reductions in lactate dehydrogenase (LDH) levels, transfusion requirements, and improvements in hemoglobin levels and fatigue scores[19]. These findings suggest that Danicopan may effectively complement existing C5 therapies by targeting residual hemolysis and improving overall disease control in PNH patients with EVH. Danicopan is an oral small molecule inhibitor of the complement factor D, a key component of the alternative pathway of the complement system. It works upstream of C5 inhibition, potentially offering a novel approach to controlling hemolysis in PNH[20].

In summary, while current treatments such as C5 inhibitors have significantly improved outcomes for PNH patients, there remains a subset of individuals who experience extravascular hemolysis despite optimal therapy[21]. Danicopan represents a promising add-on treatment option that may help address residual hemolysis and further optimize disease control in these patients. Danicopan as an add-on therapy to complement inhibitors like Soliris or Ultomiris aims to fill the gaps in treatment by providing additional inhibition of the alternative pathway, thereby targeting extravascular hemolysis and potentially reducing the need for blood transfusions while improving overall clinical outcomes in patients with PNH[22].

5. Improved Outcomes

Patients, caregivers, and families affected by paroxysmal nocturnal hemoglobinuria (PNH) may have several desired improvements in a new treatment like Danicopan, especially considering its role as an add-on therapy to complement inhibitors like Soliris or Ultomiris. Here are some potential improvements they may hope for:

- Further Reduction in Hemolysis Symptoms: While current treatments like Soliris or Ultomiris have significantly improved outcomes by targeting the terminal complement pathway, some patients still experience residual hemolysis symptoms,

including fatigue, shortness of breath, and pain. They may desire a treatment that provides even greater control over these symptoms, addressing both intravascular and extravascular hemolysis more comprehensively.

- Reduced Dependency on Blood Transfusions: Despite treatment with complement inhibitors, some patients with PNH may still require regular blood transfusions due to ongoing hemolysis and anemia. Patients and caregivers may hope for a new treatment that further reduces or eliminates the need for blood transfusions, thereby improving convenience, reducing the risk of transfusion-related complications, and enhancing overall quality of life.
- Improved Long-Term Outcomes: Patients and caregivers may desire a treatment that not only controls symptoms in the short term but also offers the potential for long-term disease management and improved overall prognosis. They may hope for a treatment that not only addresses current symptoms but also slows disease progression, reduces the risk of complications such as thrombosis, and enhances long-term quality of life.

In terms of daily life and quality of life, if a new treatment like Danicopan were to provide these desired improvements, patients, caregivers, and families may experience several positive changes. These could include:

- Reduced symptom burden, leading to improved energy levels, physical functioning, and overall well-being.
- Decreased reliance on medical interventions such as blood transfusions, resulting in greater independence and freedom from treatment-related restrictions.
- Enhanced ability to engage in daily activities, work, and social interactions without being limited by the symptoms and complications of PNH.
- Improved emotional well-being and reduced anxiety related to disease management, knowing that their condition is better controlled with the new treatment.

In summary, patients, caregivers, and families affected by PNH desire treatments that offer improvements in symptom control, treatment burden, and quality of life, beyond what is achieved with currently available C5 therapies. A treatment like Danicopan, with its potential for oral administration and add-on use with existing C5 therapies, could address these unmet needs and significantly impact the daily lives and well-being of individuals affected by PNH. However, they will carefully evaluate the potential benefits, risks, and trade-offs to make informed decisions about their therapy choices.

6. Experience With Drug Under Review

The patient we interviewed was diagnosed with Paroxysmal Nocturnal Hemoglobinuria (PNH) in 2018 after a long and challenging journey involving various diagnoses and consultations with numerous specialists. Unfortunately, after starting on Ultomiris, it became evident that she was experiencing EVH issues. Despite being on treatment, she continued to feel very exhausted, experienced brain fog, and struggled to care for her young baby. This not only impacted her physical health but also her ability to fulfill her role as a mother effectively. However, when her specialist enrolled her in a clinical trial for Danicopan, she experienced a remarkable improvement in her symptoms. Almost immediately, she felt like she did years before being diagnosed with PNH.

Controlling EVH for patients like the one described is paramount for ensuring their safety and well-being. EVH initiatives help pharmaceutical companies provide comprehensive care beyond clinical outcomes, addressing symptoms such as fatigue and cognitive impairment. By supporting EVH initiatives and prioritizing patient experiences, pharmaceutical companies demonstrate their commitment to improving patient safety and outcomes. Patients who experience significant improvements in their quality of life because of innovative treatments become advocates for the company and its products, contributing to long-term success and patient loyalty.

Understanding patients' experiences and perspectives is crucial for evaluating the clinical efficacy, tolerability, and impact of new therapies in the management of PNH. In this context, the evaluation of Danicopan, an oral factor D inhibitor, by CADTH necessitates a comprehensive examination of patient insights. Patients' individual experiences with Danicopan offer valuable insights into how the drug meets their needs, preferences, and treatment goals, thereby informing the assessment of its value as a new therapeutic option for PNH. By exploring various aspects such as access to the drug, benefits compared to previous therapies, disadvantages, impact on daily life, ease of use, subgroups of patients who may benefit, sequencing of therapies, and key values important to patients and

caregivers, CADTH can gain a holistic understanding of Danicopan's role in PNH management from a patient-centric perspective. This analysis facilitates evidence-based decision-making and ensures that patients' voices are central in the evaluation process.

Benefits Compared to Previous Therapies: Patients may have experienced various benefits with Danicopan as an add-on to C5 inhibitors (e.g., Eculizumab or Ravulizumab) compared to C5 inhibitors alone (e.g., Soliris or Ultomiris). Danicopan's mechanism of action as an oral factor D inhibitor offers additional hemolysis control beyond the inhibition of terminal complement activation achieved with C5 inhibitors alone. Similarly, Pegcetacoplan, a novel stand-alone investigational therapy, exudes existing treatments by targeting the complement cascade at the level of C3, which represents a distinct approach compared to C5 inhibition. By inhibiting factor D or targeting C3, Danicopan can intervene at critical points in the complement cascade, potentially resulting in a more comprehensive suppression of hemolysis and associated complications[25].

By targeting the alternative complement pathway, Danicopan as an add-on to either Soliris or Ultimoris may further reduce hemolysis and its associated complications, leading to improved clinical outcomes for PNH patients. This approach may result in synergistic effects, including a more pronounced reduction in lactate dehydrogenase (LDH) levels, decreased transfusion requirements, elevated hemoglobin levels, and enhanced quality of life compared to treatment with C5 inhibitors alone[27].

Disadvantages and Impact on Daily Life: While Danicopan may offer benefits, patients may also experience disadvantages such as potential side effects or tolerability issues. Common side effects reported in clinical trials include gastrointestinal symptoms and liver enzyme elevations[28]. These side effects could impact patients' daily activities and overall well-being, potentially necessitating adjustments to treatment regimens or additional medical management.

Subgroups of Patients Benefitting from Danicopan: Certain subgroups of PNH patients, particularly those with clinically significant EVH despite treatment with C5 inhibitors, may derive particular benefit from Danicopan. Danicopan's mechanism of action as a factor D inhibitor may address residual hemolysis in these patients and improve overall disease control[30].

Summary Statement of Key Values: Key values important to patients and caregivers regarding Danicopan may include improved disease control, reduced treatment burden, enhanced quality of life, and better tolerability compared to previous therapies. These values reflect the overarching goal of optimizing patient outcomes and well-being in the management of PNH.

In summary, understanding patients' experiences with Danicopan is essential for evaluating its clinical efficacy, tolerability, and impact on daily life in the management of PNH. By considering patients' perspectives, CADTH can better assess the value of Danicopan as a new therapeutic option for PNH.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

As CADTH undertakes the review of Danicopan for the management of PNH, it is imperative to consider various aspects that contribute to a comprehensive evaluation of this novel therapeutic option. Danicopan, an oral factor D inhibitor, represents a potential advancement in the treatment landscape for PNH, offering a targeted approach to complement inhibition beyond existing therapies such as C5 inhibitors (e.g., Eculizumab, Ravulizumab). In conducting this review, CADTH reviewers and the expert committee must delve into multiple facets, including the drug's mechanism of action, small size clinical trial data, long-term safety, and efficacy yet to be determined, patient-reported outcomes, cost-effectiveness, unmet needs, regulatory status, and emerging data. By examining these key elements, CADTH can provide evidence-based recommendations regarding the use of Danicopan in the management of PNH, ensuring that patients, caregivers, and healthcare professionals have access to the most up-to-date and relevant information to guide treatment decisions.

The findings from the 24-week and extended period (LTE) of the vital ALPHA Phase III trial bring encouraging news for individuals living with PNH. Results showed that adding Danicopan to the standard treatment with Ultomiris or Soliris provided ongoing clinical improvements for patients experiencing EVH. This underscores the potential of Danicopan to enhance the quality of life for those battling PNH.

Mechanism of Action: Danicopan inhibits factor D, a key component of the alternative complement pathway. By targeting this pathway, Danicopan modulates complement activation and reduces hemolysis in patients with PNH[31]. Understanding the mechanism of action is essential for assessing its therapeutic potential and safety profile.

Clinical Trial Data: Reviewers should thoroughly evaluate data from clinical trials, including efficacy, safety, and tolerability outcomes. This includes analyzing data from phase 3 trials such as the ALPHA trial, which assessed the efficacy of Danicopan as an adjunctive therapy to C5 inhibitors in patients with PNH[32].

Long-term Safety and Efficacy: Consideration should be given to the lack of long-term safety and efficacy data of Danicopan. Although short-term clinical trial data may demonstrate promising results, long-term follow-up studies are crucial for assessing the durability of treatment response and identifying any potential safety concerns[33].

Patient Reported Outcomes: CADTH should also examine patient-reported outcomes (PROs) to assess the impact of Danicopan on patients' quality of life, functional status, and treatment satisfaction. The one PRO we were able to source provided invaluable insights into the patient experience, which is something CADTH should highly consider into their review.

Unmet Needs and Patient Preferences: In evaluating Danicopan, it's crucial for CADTH reviewers to assess how effectively it addresses the unmet needs of patients with PNH. This includes considerations such as the treatment's ability to provide comprehensive symptom control, reduce treatment burden, and improve overall quality of life beyond what is currently available[34]. Additionally, understanding patient preferences regarding treatment attributes such as route of administration, frequency of dosing, and side effect profile is essentia[35]. By incorporating patient perspectives into the evaluation process, decision-makers can better tailor treatment options to meet the diverse needs and preferences of individuals living with PNH[36].

EVH Status: there is an important aspect related to the treatment of paroxysmal nocturnal hemoglobinuria (PNH) that warrants consideration in this drug review. Despite the significant advancements made with C5 inhibitors such as Soliris and Ultomiris in managing intravascular hemolysis (IVH) and thrombosis in PNH patients, there remains a subset of individuals who continue to experience clinically significant extravascular hemolysis (EVH) while on these therapies. This unmet need underscores the importance of exploring additional treatment options, such as Danicopan, as adjunctive therapy for patients with PNH and EVH despite being on Soliris or Ultomiris.

Providing patients with alternative treatment options is crucial for addressing their individualized needs and optimizing outcomes. By evaluating the efficacy and safety of Danicopan in this context, CADTH reviewers and the expert committee can ensure that PNH patients have access to a comprehensive range of therapies tailored to their specific disease manifestations. Additionally, assessing the potential benefits of Danicopan in reducing EVH alongside current standard-of-care treatments like Soliris or Ultomiris can offer valuable insights into its role in improving overall disease management and patient well-being[37].

The interviewed patient asked that we share a message with you: “We need options beyond infusions because they are not enough. Patients deserve equitable access to care and treatment, and to feel 'normal'. This can only happen if we can access innovative treatments in a timely manner. Decision-makers, like yourself, should consult patients like me before making decisions that could negatively impact our lives. Without walking in our shoes, it's impossible to grasp the frustration of yearning for a normal life yet feeling tethered by the challenges of poorly controlled symptoms stemming from PNH/EVH. I want to be the best mother I can be, it's my right, just like it's my right to access Danicopan.”

By considering these factors, CADTH reviewers and the expert committee can conduct a comprehensive evaluation of Danicopan and provide evidence-based recommendations regarding its use in the management of PNH.

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Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
Yes, consultant (Hanzo Pharma & Biotech Consultant)

1. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it. Yes, consultant (Hanzo Pharma & Biotech Consultant)
2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alexion			X (direct interest)	
Novartis			X	
Roche		X		
Sobi			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Barry Katsof

Position: President & Founder
Patient Group: The Canadian Association of PNH Patients
Date: 4/5/2024

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie		X		
Alexion				X (direct interest)
BMS			X	
Sobi			X	
Regenron			X	
Taiho		X		
Roche		X		
Novartis			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Cindy Anthony
Position: Executive director
Patient Group: AAMAC
Date: 4/5/2024

Clinician Input

CADTH Project Number: SR0815-000

Generic Drug Name (Brand Name): DANICOPAN

Indication: Add-on to ravulizumab or eculizumab for treatment of extravascular hemolysis (EVH) in adult patients with PNH

Name of Clinician Group: Canadian PNH Network

Author of Submission: Dr. C. Patriquin, with contribution and editorial support by the cosignatories of this document

1. About Your Clinician Group

The Canadian PNH Network is a group of Canadian hematologists with a special interest and expertise in the care of patients with paroxysmal nocturnal hemoglobinuria (PNH). Members represent centres of excellence from Newfoundland, Nova Scotia, Quebec, Ontario, Alberta, and British Columbia. The Canadian PNH Network sites follow the vast majority of PNH patients in Canada, either directly or as part of shared-care relationships with community physicians. We also set consensus for diagnosis and management of PNH in the country (Patriquin CJ et al. [2019] Eur J Haematol) and serve as sites for ongoing observational and interventional research activities both nationally and internationally.

2. Information Gathering

Information for this submission was obtained via publicly available documents, congress abstracts, and the published literature (including the ALPHA trial – Lee JW et al. [2023] Lancet Haematology). Standard of care data were similarly obtained, and the members of the Canadian PNH Network were invited to contribute to the various segments.

3. Current Treatments and Treatment Goals

The current standard of care (SOC) for patients with hemolytic PNH is terminal complement inhibition with C5 blockade. Eculizumab, and more recently ravulizumab, remain the only first-line therapies across the country. To be approved for eculizumab or ravulizumab in Canada, patients must have evidence of a PNH clone ≥ 10%, lactate dehydrogenase (LDH) > 1.5 x the upper limit of normal (ULN), and at least one significant clinical manifestation such as thrombosis, anemia, transfusion-dependence, renal or respiratory failure without other explanation, and smooth muscle dystonic symptoms requiring either hospitalization or opioid analgesia.

The only curative treatment for PNH is allogeneic hematopoietic stem cell transplant. It should be noted, however, that this is reserved for patients with predominant or progressive bone marrow failure (e.g. aplastic anemia), which can coincide with, precede, or follow a diagnosis of PNH. Transplant is not recommended for all patients given the increased risk of complications and transplant-related mortality compared to C5 inhibition. Though complement inhibition does not address the underlying marrow mutations which cause PNH, complement blockade and associated control of intravascular hemolysis (IVH) leads to significant improvement in quality of life, fatigue, transfusion-dependence, thrombosis, and overall survival. Supportive therapies for PNH patients, if needed, include hematinic support (folate, iron), analgesia, and anticoagulation either to treat or protect against thrombosis. It should be noted, however, that anticoagulation alone does not protect against thrombosis in PNH, which is the leading cause of death in untreated patients (40-67%).

Treatment with C5 inhibition, such as with eculizumab/ravulizumab, is highly effective at controlling intravascular hemolysis. This is measured by targeting an LDH <1.5 x ULN. Associated with this, we would watch for improvement in hemoglobin, reduced transfusion needs, and absence of other end-organ complications like thrombosis, renal failure, and pulmonary hypertension. With C5 inhibition, PNH red cells are now able to survive and circulate where previously they would have been exquisitely sensitive to terminal complement-mediated IVH. Now that red cells survive, they can have more and more C3 split products (e.g. iC3b, C3dg) bind to their membranes. As cell-bound complement inhibitors are missing, the dense C3 deposits drive extravascular hemolysis, mostly via receptors in the liver. Because of this, about a third of PNH patients remain symptomatically anemic and possibly still

transfusion-dependent (Debureaux P et al. [2021] Bone Marrow Transplant), with increasing rates of extravascular hemolysis coinciding with reduced levels of hematologic response. Due to the underlying disease phenotype, any C5 inhibitor can drive the extravascular hemolysis. In contrast, blocking complement at a proximal level, such as C3 by pegcetacoplan, this extravascular hemolysis is also blocked, allowing for increased hemoglobin.

Pegcetacoplan has been recently approved in Canada and is publicly available in several provinces. This is a twice-weekly subcutaneous infusion (typically self-administered) which is indicated for patients with persistent anemia despite at least 6 months of C5 inhibitor-based therapy or should they be intolerant to C5 inhibitors. In the PEGASUS trial (Hillmen et al. [2021] NEJM), patients receiving pegcetacoplan had a significant improvement in change-from-baseline hemoglobin, which has been sustained now out to 3 years of follow-up (de Castro et al. [2023] ASH abstract / Patriquin et al. [2024] Advances in Therapy, in press).

Please note that a general therapeutic approach to patients with PNH with a Canadian focus can be found in our consensus guidelines (Patriquin CJ et al. [2019] Eur J Haematol) and recent review (Oliver M & Patriquin CJ [2023] J Blood Medicine).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Breakthrough hemolysis (BTH) is a complication of PNH therapy in which (due to insufficient dosing, exposure to complement-amplifying conditions, or both) there is a return of IVH, typically detected by elevated LDH, anemia, return/exaggeration of symptoms, and possibly significant drops in hemoglobin. This can occur with incomplete blockade at C5 in the case of terminal complement inhibitors. By using proximal complement inhibitors, the pool of circulating PNH red cells increases as they avoid both intravascular and extravascular hemolysis, thus beneficially leading to increases in hemoglobin while theoretically increasing the potential for a significant drop in hemoglobin in cases of BTH. Indeed, if there is incomplete proximal complement blockade, complement activation can occur in an enzymatic cascade (i.e. each unblocked molecule may lead to activation of downstream complement activity with membrane attack complex formation), leading to severe hemolysis. For this reason and other mechanisms outlined by Notaro and Luzzatto (NEJM 2022), outcomes of BTH with proximal complement inhibitors may be more severe than episodes on terminal complement inhibitors, a finding supported by some trial data and anecdotal clinical experience. A clinical trial assessing a twice-daily anti-Factor D drug (vemircopan) as monotherapy was terminated early due to concerns over higher reported rates of BTH compared to other trials, despite promising results from phase II data (Browett et al., [2022] ASH poster). As the pegcetacoplan data mature, with now 3 years of follow-up for the PEGASUS data, approximately 30% of patients have physician-reported BTH. As was seen in the PEGASUS trial supplementary data, some patients on pegcetacoplan have had significant breakthrough with LDH values 10-15x ULN and profound drops in hemoglobin from hemolysis. In such cases, intensified dosing of pegcetacoplan is needed, at least temporarily, to address the BTH (Griffin M et al., Blood Advances 2024).

The delivery mechanism for pegcetacoplan, as mentioned, is a self-administered subcutaneous infusion that can take 30-60 minutes. Most patients take this twice weekly, though if they have incomplete control, some require escalation to every-3-day or even thrice-weekly dosing. This can be challenging for some, including patients with needle phobia, vision problems, poor skin integrity, and/or issues with manual dexterity, and the product must also be kept refrigerated (including in the context of travel).

There is a subset of patients who would benefit from proximal complement inhibition given the development of clinically significant EVH, but for whom pegcetacoplan is less than ideal. Most importantly, some patients have repeated BTH on proximal complement inhibition as monotherapy, and would be protected from complications of IVH (e.g. thrombosis, kidney failure) by having dual complement blockade (i.e. anti-C5 plus a proximal inhibitor). The additional proximal blockade would provide the patients the same benefits of improved hemoglobin, but with a lower risk of complications (as was seen in the ALPHA trial but Lee et al. [2023] in Lancet Haematology). Especially with ravulizumab now available in Canada, the patient treatment burden can also be reduced significantly by switching from fortnightly to every-8-week intravenous dosing, to help off-set the thrice daily danicopan oral therapy. As an example, one of us had a patient in the vemircopan trial who developed massive BTH with anemia and acute kidney injury, necessitating intensive care unit admission. She thankfully recovered with aggressive supportive care, though continued to have intermittent episodes of less severe BTH. She has since been switched to compassionate ravulizumab plus danicopan and no longer experiences these events.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Danicopan is a thrice-daily oral Factor D (proximal complement) inhibitor which has shown significant improvements in hemoglobin in patients with suboptimal response to C5 inhibition alone (i.e. eculizumab, ravulizumab). Of note, in the placebo-controlled ALPHA trial, all patients were transfusion-dependent at the start. With the addition of danicopan, over 80% were transfusion-free at 12 weeks, and this continued out to 24 weeks as well (78-90%) (Lee et al. [2023] Lancet Haematol / Kulasekararaj et al. ASH 2023 - oral 576 / Lee et al. EHA 2023 - poster 771). This combination would be used in patients as per ALPHA protocol, for those with persistent anemia despite C5 inhibition, in whom EVH is suspected. It would be expected to work for any such patient with symptomatic and/or transfusion-dependent anemia felt related to EVH, even with higher hemoglobin values that those used in the trial (i.e. the same patient population as approved for pegcetacoplan). It could also provide another option for patients who may receive proximal inhibition monotherapy (e.g. pegcetacoplan) who may not tolerate it or have repeated BTH or other concerns.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As described above, and as seen in ALPHA, the patients most likely to benefit from pegcetacoplan are those who have persistent anemia despite stable-dose eculizumab or ravulizumab. These patients with extravascular hemolysis currently have limited options to improve their hemoglobin concentration. The recent approval of C3 inhibition in Canada now provides one option; however, there may be some patients with suboptimal hemoglobin response who may not be best served by pegcetacoplan (e.g. needle phobia, poor manual/visual dexterity to self-administer the drug, hypersensitivity/allergy). In addition, some patients with a history of PNH-related thrombosis or who go on to experience severe and/or repeated BTH episodes may be better served by maintaining a base of direct C5 inhibition (e.g. with ravulizumab) whilst adding a proximal inhibitor to support improved hemoglobin values and transfusion-independence.

It is of course important that clinicians assess for other causes of ongoing anemia as well (e.g. bleeding, bone marrow failure, BTH), but this is easily done with standard history taking and laboratory testing. Pharmacokinetic BTH can be identified in patients with cyclical symptoms leading up to their next C5 inhibitor infusions who may also show increased LDH and CH50 values. Patients with bone marrow failure would likely show evidence of decreasing reticulocyte and platelet counts (this could be confirmed with bone marrow biopsy/aspiration in unclear cases but not required). Extravascular hemolysis is typically suspected in PNH patients on C5 inhibition who have persistent reticulocytosis, indirect hyperbilirubinemia and with minimal LDH elevation. This must all be taken together in the individual patient context, as concomitant marrow failure (not uncommon in PNH) may blunt the reticulocytosis, as example, and obscure EVH. There are some additional findings that may support EVH as a contributor to anemia, such as C3d loading found on direct antiglobulin testing, but this is not yet a validated test for this clinical situation. As with the PEGASUS trial of pegcetacoplan, it was not needed in ALPHA either, yet most patients saw significant improvements.

PNH patients least suitable would be those who are not anemic, who meet exclusion criteria otherwise as used in the ALPHA trial, and particularly those planning to get pregnant as do not have safety data (as compared to eculizumab alone, where we have evidence to support its efficacy and safety in this context – Kelly R et al. -2015] NEJM).

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response to complement blockade in PNH patients first and foremost focuses on reduction in LDH, which is a consistent surrogate used to identify intravascular hemolysis activity. The goal is to have patients consistently fall below an LDH ratio of 1.5x the ULN. This not only reduces hemolysis and may improve hemoglobin and transfusion-dependence, but it also reduces the risk of thrombosis in PNH. Clinical outcomes related to this, as seen in the landmark eculizumab and ravulizumab trials, are decreased fatigue, transfusion requirements, improved QoL and, given the maturity of eculizumab data available, also improved overall survival. An important outcome of clinical (and clinical trial) interest is an increase in hemoglobin, particularly now that there are proximal inhibitors. As danicopan would be an add-on therapy, particularly for patients with suboptimal hemoglobin response to C5 inhibition alone, most patients would already have control of their LDH to <1.5x ULN.

A clinically meaningful response to treatment would be sustained control of LDH but with further hemoglobin increases and improvement in anemia-related symptoms. Transfusion-dependence would also be a key parameter to measure, as long-term transfusions can be harmful and are also a significant burden on the national blood supply and health care resources in general. The

increase in hemoglobin in danicopan-treated patients is quite objective and not expected to vary across physician treaters. In fact, rather similar increments around 20-30 g/L have been seen not just in ALPHA but in trials of other proximal inhibitors targeting complement factors B (iptacopan) and C3 (pegcetacoplan). Supporting data to show reduced EVH +/- IVH also include a reduction/normalization of reticulocytes and indirect hyperbilirubinemia. Efficacy outcomes would typically be followed every 2-4 weeks initially, but follow-up would be required less often (e.g. every 3-6 months) as a patient becomes established on the drug and dose not show evidence of side effects or other concerns. Of note, dose escalation for danicopan was needed in approximately 60% of patients in the trial, so more a lack of improvement in the first few months of therapy would be a prompt to dose-increase.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Danicopan discontinuation should be considered in patients who have adverse events that preclude ongoing therapy. This may include issues with poor compliance or intolerable side effects (this is not common based on the trial data). Elevations in liver enzymes were seen in the ALPHA trial, with some patients needing to stop the drug if severe and/or not resolving. Other intolerances or side effects would also prompt a discussion about either dose-reduction or discontinuation on a case-by-case basis. The most important feature to watch for is evidence of BTH. It is possible that some patients who take danicopan will have significant expansion of their circulating red blood cells and, in situations of severe complement-mediated stress, could have increased hemolytic events. However, with a baseline of direct anti-C5 inhibition with ravulizumab or eculizumab, which would be continued regardless, the significance of this should be much less than has been seen in some patients receiving C3 inhibition. Lastly, any patient who becomes pregnant and/or was breastfeeding would need to have their danicopan stopped temporarily, at least for now, as there are no safety data in this context.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

PNH is an ultrarare disease with nuances to diagnosis, treatment, and overall management. Patients likely benefit being followed by clinicians who specialize in the area, particularly once we are considering patients for second/later-line therapeutic strategies. Members of the Canadian PNH Network would certainly be included in this categorization. Monitoring of patients can be done with standard laboratory investigations and clinical visits. However, specifically regarding treatment with danicopan plus C5 inhibition, this is done entirely at the patient's home (or the C5 inhibitor infusions could be given at an infusion clinic or hospital based on local/provincial practices). Patients can even travel with their drug, especially with a switch from eculizumab to ravulizumab for the C5 inhibitor.

6. Additional Information

We believe that the submission above addresses the various points, data, and clinical opinions we hope to convey.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

3. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   We did not.

4. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   We did not.

5. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Christopher Patriquin

Position: Assistant Professor of Medicine (Hematology), Clinician Investigator, University Health Network / Chair, Canadian PNH Network

Date: 26 March 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion			X	
Sobi			X	
Novartis		X		
Roche		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Monika Oliver

Position: Hematologist, University of Alberta

Date: 12-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		X		
Novartis		X		
Roche	X			
Sobi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Brian Leber

Position: Professor of Medicine (Hematology), McMaster University

Date: 12-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion	X			
Sobi		X		
Novartis		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Danièle Marceau

Position: Laboratory Medical Director, Chaudière-Appalaches, Province de Quebec

Date: 19-03-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion/Astra Zeneca		X		
Roche		X		
Sobi		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Thomas Nevill

Position: Clinical Director, Leukemia / BMT Program of British Columbia

Date: 20 March 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		X		
Novartis		X		
Sobi		X		
Taiho		X		
Celgene/BMS		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Catherine Sperlich
Position: Hematologist, Chief of hematology-oncology, Hôpital Charles-Lemoyne, Greenfield Park, QC; clinical professor, Université de Sherbrooke; member of the Canadian PNH group
Date: 20 March 2024
☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		X		
Sobi		X		
Novartis		X		
Roche	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Marc Nicolas Bienz
Position: Hematologist, Jewish General Hospital, Montreal/Assistant professor, McGill University
Date: 23 March 2024
☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion	X			
Sobi	X			
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Kuljit Grewal
Position: Associate Professor of Medicine, Memorial University of Newfoundland
Date: 24 March 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		X		
Sobi		X		
Novartis		X		
Roche		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Jennifer Grossman
Position: Hematologist, Foothills Medical Center, Calgary, Alberta
Date: 1 April 2024
☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
No disclosures				

* Place an X in the appropriate dollar range cells for each company.