CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

maralixibat (Livmarli)

(Mirum Pharmaceuticals Inc.)

Indication: Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).

November 2, 2023

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	Alberta Children's Hospital, Pediatric Liver Centre, Calgary
Contact informationa	Name: Dr. Simon Lam, Pediatric Hepatologist [redacted] Dr. Simone Kortbeek, Pediatric Hepatologist [redacted] [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No IZI

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Dr. Kortbeek and I are speciality trained pediatric hepatolgist with extensive experience caring for children with Alagille syndrome (ALGS). We care for all children with ALGS in southern Alberta and the Eastern Kootenays in British Columbia. Intractable pruritus is a well-known complication of ALGS. We have number of patients with severe pruritus leading to poor sleep, poor school performance, significant cutaneous excoriations and self mutilation. It is also typical for the parents' sleep and quality of life to be greatly affected as the itchy child will go to his/her parent's bed in the middle of the nigh to be comforted.

In regard to the effect of maralixibat on improved quality of life (pg. 4). A recent study showed clinically meaningful improvement in pruritus and health related quality of life in children with ALGS treated with maralixibat (PMID: **36096175).** In addition, patients who responded to maralixibat also had improved family impact scores and fatigue scores. We feel this study also addresses the concern regarding frequency and severity of pruritis, reduced patient and caregiver fatigue (pg. 3).

Prior to the advent of ileal bile acid transporter inhibitors (IBAT), treatment for cholestatic pruritus included ursodeoxycholic acid, rifampin, naltrexone, sertraline or cholestyramine. However, use of these therapies are based on anecdotal experience or small case series. Furthermore, some of the medications can be hepatotoxic or very poorly tolerated, rifampin and cholestyramine, respectively. To our knowledge, maralixibat is the only medication that has been studied in a randomized control trial to show significant improvement in pruritus and positively impact quality of life (PMID: **34755627 and 36096175).**

Regarding the concern of long-term efficacy and safety (pg. 15), our program has firsthand experience with maralixibat treating patients with cholestatic pruritus. We have found this medication safe with only minor side effects. In responders, the impact has been remarkable. These patients were now able to sleep through the night, and no longer have self-mutilating behavior related to the intense unrelentin itch. The arents of these atients also saw si nificant im rovement in uali of

life in regard to improve energy, attention span, and general wellness. Similarly, parents of these children also felt there was a significant improvement in their quality of life as well because their child was no longer waking up in the middle of the night due to itching. Our colleagues have referred to this class of medications as "transformative".

We acknowledge that real-world long-term efficacy/safety data is lacking, however data from the ICONIC trail showed sustained efficacy and safety up to 204 weeks (PMID: **34755627).** As noted by CDEC (pg. 4), the long-term extension used higher doses (760mcg/kg/day), but despite this dose increase, safety was still preserved. This shows a good safety profile both at the lower dose 380mcg/kg/day) and higher dose (760mcg/kg/day) of maralixibat. It is not clear why CDEC feels otherwise. From our clinical experience, current off-label treatments of cholestatic pruritus typically do not have sustained long-term benefit.

We strongly disagree with CADTH's recommendation not to reimburse this treatment despite strong recommendations to reimburse from all pediatric liver specialists across Canada who care for these patients on a daily basis and see firsthand the transformative impact of this medication.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	IZI

If not, what aspects are missing from the draft recommendation?

If the recommendation of the experts in hepatology or pediatric hepatology were considered for the management in cholestatic pruritus in children with ALGS, the recommendation would have been Recommend Reimbursement with clinical criteria and/or conditions. There is unanimous support from the Canadian pediatric hepatology community that maralixiabt should be reimbursed and available to our patients.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	IZI
	No	☐

If not, please provide details regarding the information that requires clarification.

Yes, but we feel that the panel's interpretation of the published literature and the positive impact on the disease is incongruent with that of the **entire** North American pediatric hepatology community.

Furthermore, AGLS is a rare disorder and trials cannot reasonably be expected to include large number of patients.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	IZI
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	IZI
	No	☐

Not applicable

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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.
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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Simon Lam
Position	Pediatric Hepatologist
Date	*31-10-2023*

	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	181	☐	☐	☐
Medison	181	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	Dr. Simone Kortbeek
Position	Pediatric Hepatologist
Date	*31-10-2023*
181	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.

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None	☐	☐	☐	☐

CADTH

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Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	University of Alberta, Alberta Transplant Institute, Edmonton, AB
Contact informationa	Name: Dr. Susan Gilmour [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No ☒

On behalf of the Pediatric Hepatology section at the University of Alberta and as a Professor of Pediatrics, Pediatric hepatologist for over 26 years and Director of the Western Canadian Pediatric Liver transplant program, we have had to honour and opportunity to provide specialized clinical care to many children with Alagille's syndrome and therefore have had extensive experience in the limited clinical care, outside of liver transplant, currently available for these patients.

Effective clinical management of debilitating symptom, pruritus of cholestasis, in Alagille's syndrome is a significant gap in our current clinical management of children with this disorder. CADTH's recommendation to not reimburse marilixibat will result in harm to Canadian children with rare inherited cholestatic liver diseases and disadvantage them compared to their peers in both the United States and Europe. As quaternary referral Pediatric Hepatologists at the University of Alberta, we do not agree with the CDEC's recommendation to "not reimburse". Noted below is our review and response to the CDECreview.

Alagille's is a very rare disorder, which often ends up in early liver transplantation (an exclusion criteria for the ICONICtrial) and as such clinical trials will never have large numbers of patients, as has been noted for all rare diseases (1). The ability to have a randomized phase 3 trial for such disorders is not typical and significant positive evidence, including the reduction of sBA, is transformative for our patients and practice.

The University of Alberta, Pediatric Hepatology section, does use serum bile acids (sBA)as a clinical biochemical marker, as do most other Pediatric hepatologists, to assess the severity of cholestasis and correlation with pruritus and the reported and physical examination. While not a linear marker of cholestasis, accumulation of sBA does correlate with severity of pruritus. (2). Maralixibat has been demonstrated, in the ICONIC trial, to make a clinically significant decrease in the predominant symptom of itch, patient, family and clinician reported and a clinical meaningful difference IS evidence for efficacy in this disease.

Expert reviewers for CADTH agreed that there is a significant gap in our ability to treat the debilitating outcome of itch and that it impacts sleep, appetite, school performance and family function. Families have spoken of this "itching from inside, which is torture" to the media (Global News, Su-Long Goh, Health Matters, October 5, 2022). The ICONICtrial did demonstrate a clinically meaningful improvement in pruritus and improved quality of life. The ability of marilixibat to improve this current gap in therapy will make a clinically

significant improvement in quality of life, as was demonstrated using the well validated and accepted tool, Peds QL (Varni). Improvements in a validated tool do constitute evidence for meaningful improvement in QOL.

Expert reviewers noted the potential to improve transplant free survival. This was demonstrated with the comparison to a subcohort of the GALA (3) study. CDEC stated that this was not robust evidence but did not comment on the evidence of sBA accumulation in the liver to result in cell injury, fibrosis leading to end-stage liver disease and progression to LT. (4) Indicating the importance of decreasing sBA in the treating cholestatic liver disease.

As Canadian experts in the care of patients with Alagille's syndrome, our section, respectfully requests a review and revision of the initial CDEC/CADTH recommendation of "do not reimburse" in light of the evidence and experience of marilixibat's transformative clinical effect on thispatient population.

1. https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement/discussion-paper.html
2. Pruritus in cholestasis: Facts and fiction. Hepatology: 29 Oct 2013
3. Natural hstory of liver disease in a large international cohort od children with Alagille's syndrome: Results from the GALA study. Hepatology 1 Feb 2023; 77(2): 512-529
4. The role of bile acids in cholestatic liver injury. Ann Transl Med; 9 Apr 2021: 9(8): 737

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

As members of CASL, there was unanimous and strong support by all Pediatric Hepatologists for the approval of marilixibat. As the physicians who care for these patients, we have a keen understanding of how debilitating pruritus of cholestasis is, we have reviewed the evidence as published and presented at scientific meetings and many have experience through Health Canada's special authorization program, for clinical use.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

As noted above, the evidence of the correlation of sBA and pruritus were not referenced nor was the evidence of bile acid progressive damage to hepatocytes and the pathophysiology of why an increased event free survival (transplant/death) is supported with the use of an iBAT inhibitor

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

a CADTH may contact this person if comments require clarification.

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	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	○
If yes, please detail the help and who provided it.		

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	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed:		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Susan Gilmour
Position	Professor Pediatrics, Director Pediatric Liver Transplant at University of Alberta, Edmonton, AB
Date	*26-10-2023*
	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.
Conflict of Interest Declaration	

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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50.000**
Mirum		☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dr. Patricia Kawada
Position	Pediatric Gastroenterologist, Clinical Lecturer in the Department of Pediatrics
Date	*26-10-2023*
	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.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50.000**
nla	D	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	Dr. Kerry Wong
Position	Pediatric Gastroenterologist
Date	*26-10-2023*
	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.

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nla	D	☐	☐	☐
	☐	☐	☐	☐

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Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).
Organization	CANADIAN PEDIATRIC HEPATOLOGY RESEARCH GROUP, CANADIAN ASSOCIATION FOR THE STUDY OF THE LIVER **(CASL),** SPECIAL INTEREST GROUP **MEMBERS OF THE GROUP AND AUTHORS OF FEEDBACK:** Carolina **Jimenez** [redacted] **IIIIIIIIIIII!(Chair)** Andreanne Zizzo [redacted] Ashok Dandhapani [redacted] Binita Karnath [redacted] Eve Roberts [redacted] Herbert Brill [redacted] Jeff Critch [redacted] Mohit Kehar [redacted] Mohsin Rashid [redacted] NajmaAhmed [redacted] Patricia Kawada [redacted] Pushpa Sathya [redacted] Rick Schreiber, [redacted] Simon Ling [redacted] Susan Gilmour [redacted] Vicky Ng [redacted] Simon Lam [redacted] Quais Mujawar [redacted] Marie-Eve Chartier [redacted] Simone Kortbeek [redacted]
Contact informationa	Name: Binita M. Karnath [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes ☐ No IZI

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The Canadian Paediatric Hepatology Research Group **(CPHRG)** encompasses all the paediatric hepatologists in Canada. As a group we are dismayed by the draft recommendation and strongly disagree with it. This recommendation will disadvantage Canadian children with Alagille syndrome (ALGS) and will unfairly restrict their access to a drug that has tremendous proven benefit for reduction of pruritus and improvement in quality of life, as well as likely benefit in delaying or preventing the need for liver transplantation. Our clinical experience with this drug demonstrates its transformative effect on children previously tortured by itch, children and parents unable to sleep, whose school and work lives are severely affected by the impact of intractable pruritus. There is no alternative agent with a proven treatment profile that is available for these children.

Page 3: Rationale for the Recommendation, Paragraph 1:

"CDEC noted that sBA is not of relevance in clinical practice since it is not often assessed due to high costs and logistical limitations, and that there is a lack of evidence validating the correlation between sBA levels and improvement in pruritis."
We disagree with this statement. Historically sBA have not been sent frequently in clinical practice, in part because we did not have a therapy that targeted sBA. As the overwhelming majority of ALGS patients are followed in hospital-based clinics with phlebotomy access sBA for this population are generally covered by hospital-based budgets and are not considered a source of significant budgetary pressure.

- There may be logistical issues with sending sBA in some smaller centres, however cost issues are not relevant in Canada. Although sBA are not sent as often as other liver labs, they are a crucial parameter in assessing degree of cholestasis. In ALGS in particular, anicteric cholestasis is a prevalent issue so a patient can have very high serum bile acids, severe pruritus and a normal bilirubin. Without measuring sBA in an ALGS patient who is not jaundiced, it is impossible to assess and document the degree of cholestasis. Serum GGT is not a good measure of degree of cholestasis. Therefore, the statement that sBA is "not of relevance in clinical practice" is simply not true.
- Despite no simple linear correlation between sBA levels and severity of pruritus, there is a very-well accepted general relationship between the two, especially in ALGS where sBA levels are often very high. We believe that pruritus in cholestasis is caused by a factor that is associated with, or a derivative of bile acids and in the current era sBA are the best available surrogate biological marker of pruritus. There is no other.

Page 3: Rationale for the Recommendation, Paragraph 1:
"CDEC noted the enrichment trial design… thus limiting the ability to assess the long-term efficacy and safety of maralixibat."

- We disagree that the long-term efficacy and safety of maralixibat cannot be assessed. As experts routinely caring for children with ALGS and using maralixibat, we can attest that this therapy has been transformative for children and their caregivers in terms of pruritus control. Further the safety profile is excellent with only very isolated instances of maralixibat being discontinued for side effects.
- From the point of view of the patient, immediate term effects (resolving pruritus) are paramount. In ALGS total-body pruritus associated with cholestasis is extremely debilitating. It interferes with activities of daily living and sleep.
- There are published long-term data which support our clinical experience: the manuscript "Impact of long-term administration of maralixibat on children with cholestasis secondary to ALGS" Shneider et al, Hepatology Communications 2022; clearly describes the long-term efficacy in terms of pruritus, quality of life and safety on 57 children with ALGS pooled from North American and UK studies, and includes children from Canada. Further this analysis was performed by an NIH-funded consortium, ChiLDReN, and independently of Mirum.

Page 4: Discussion Points, Paragraph 3:
"no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence."

- We disagree that the available evidence regarding the effects of maralixibat on quality of life are limited. The ICONIC data clearly show a positive effect. Secondly, the ICONIC quality of life data were analyzed in further detail in a separate manuscript and published; "Maralixibat treatment response in ALGS is associated with improved health-related quality of life" Kamath et al, Journal of Pediatrics 2022. Finally, the manuscript referenced above, Shneider et al, Hepatol Commun 2022 also shows improvements in quality of life in a pooled cohort of 57 patients (separate from the ICONIC cohort).

Page *14: Critical Appraisal, Paragraph 1:*
"Concerns regarding the natural history comparison include the potential residual confounding, incomparability in disease severity. and the lack of sBA data available among patients in the GALA registry."

- We disagree with these concerns. Great lengths have been taken in this statistical analysis to account for the issues listed. Based on demographics and biochemical characteristics, the two groups were balanced for disease severity. We see no basis for the stated assessment that there was "incomparability in disease severity"
- Whilst there are certainly missing sBA data in the GALA database, we performed a sensitivity analysis for the availability of sBA levels and still found the same result and therefore [redacted] was adequately met and discounted.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?

'DID'

Ifnot, what aspects are missing from the draft recommendation?

Page *7: Clinician Group Input, Paragraph 1:*

"None of the clinician group or clinical experts consulted by CADTH had declared experience with maralixibat"

- The CPHRG clinician author group has substantial experience with maralixibat. In fact we have the most experience of any physicians in Canada, including adult hepatologists.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?

[redacted]

Ifnot, please provide details regarding the information that requires clarification.

We disagree with many of the reasons for the recommendation, as stated above. Due to page limitations of this feedback document we are unable to provide further details.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	IZI D

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	IZI D

If not, please provide details regarding the information that requires clarification.

We fundamentally disagree with the rationale not to provide reimbursement for maralixibat. It appears that the principles of acceptance for common diseases have been applied to an orphan disease. The population of ALGS is small so studies will always be limited in comparison to trials in common diseases. The clinical effect of maralixibat on ALGS is large and the side effects minimal, thus any treatment with a reasonable prospect of benefit should be offered. If it saves even one liver transplant a year from happening it will more than pay for itself, and is worthy of an interim approval that could be reviewed in 5 ears for medical efficac and cost effectiveness.

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	Yes	D
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C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Carolina Jimenez, Chair- CANADIAN PEDIATRIC HEPATOLOGY RESEARCH GROUP (CASL Special Interest Group)
Position	Associate Professor and Interim Chief, Division of Gastroenterology, Hepatology and Nutrition, Director, CHEO Liver Services, uOttawa
Date	*25-10-2023*

	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.

Conflict of Interest Declaration

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None	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	Binita Karnath
Position	Division Head (interim) Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children Senior Associate Scientist, Research Institute Professor, University of Toronto Lead, CASL Canadian Pediatric Heoatoloav Research Group (CPHRG)
Date	*25-10-2023*
	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.

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	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50 000**
Mirum (Consulting + Grant funding)	☐	☐	☐	
Albireo (Consulting + Grant funding)	☐	☐	☐	

New or Updated Declaration for Clinician 3

Name	Andreanne Zizzo
Position	Division Head, Division of Paediatric Gastroenterology, Hepatology & Nutrition, London Health Sciences Center - Children's Hospital, Associate Professor, Western University
Date	*25-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum	181	☐	☐	☐
Add company name	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	Ashok Dandhapani
Position	Paediatric Gastroenterologist, Department of Paediatrics, Children's Hospital, London Health Sciences
Date	*25-10-2023*
181	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10 000	$10,001 to 50 000	In Excess of $50.000
Mirum	☐	181	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	Eve Roberts
Position	ASSOCIATE FELLOW; PROFESSOR EMERITA, UNIVERSITY OF TORONTO Pediatric Heoatoloaist, Hospital for Sick Children, Toronto, ON
Date	*25-10-2023*
181	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None	☐	☐	☐	☐
	☐	☐	☐	☐

ti'l·1i•jSrfl1•1ififOM,i¢idiMMfi,i·

Name Simon Lam

Position	Clinical Assistant Professor, Gastroenterology, Hepatology & Nutrition, Alberta Children's Hospital
Date	*25-10-2023*
rgJ	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	rgJ	☐	☐	☐
Albireo/Ipsen (Medison)	rgJ	☐	☐	☐

New or Updated Declaration for Clinician 7

Name	Herbert Brill
Position	Associate Clinical Professor, Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton, ON
Date	*25-10-2023*
rgJ	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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	rgJ	☐	D	☐
	D	☐	☐	☐

New or Updated Declaration for Clinician 8

Name	Jeff Critch
Position	Associate Professor of Pediatrics (GI}, Memorial University, St. John's, NL
Date	*25-10-2023*
rgJ	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 9	
Name	Marie-Eve Chartier
Position	Associate Professor, Division of Gastroenterology, Hepatology and Nutrition, Departement of pediatrics, CHU Sainte-Justine, Montreal, QC
Date	
rgJ	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum	rgJ	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	Mohit Kehar
Position	Pediatric Gastroenterologist and Hepatologist, CHEO - Children's Hospital of Eastern Ontario, Ottawa, ON
Date	*25-10-2023*
rgJ	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum	☐	rgJ	☐	☐
Albireo/Ipsen (Medison)	☐	rgJ	☐	☐

New or Updated Declaration for Clinician 11	
Name	Mohsin Rashid
Position	Professor of Paediatrics (Gastroenterology & Nutrition) at Dalhousie University, Halifax, NS

Date	*25-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	[gJ	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	Najma Ahmed
Position	Associate Professor Pediatrics, McGill University; Pediatric Gastroenterologist, Montreal Children's Hospital; Director Pediatrics Residency Training Program, McGill University, Montreal, QC
Date	*25-10-2023*
[gJ	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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	[gJ	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 13	
Name	Patricia Kawada
Position	Paediatric Gastroenterologist, Stollery Children's Hospital, University of Alberta, Edmonton, AB
Date	*25-10-2023*
[gJ	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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	Pushpa Sathya
Position	Associate Professor, Pediatric Hepatologist, Memorial University of Newfoundland, St. John's, NL
Date	*25-10-2023*
IZ]	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	D	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 15	
Name	Richard Schreiber
Position	Pediatric Hepatologist, BC Children's Hospital, Vancouver, BC
Date	*25-10-2023*
IZ]	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	☐	☐	☐	☐
Add company name	☐	☐	D	☐

New or Updated Declaration for Clinician 16	
Name	Simon Ling
Position	Staff Physician, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, ON; Professor, Department of Paediatrics, University of Toronto
Date	*25-10-2023*

	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	[gJ	☐	☐	☐
Albireo/Ipsen (Medison)	[gJ	☐	☐	☐

New or Updated Declaration for Clinician 17

Name	Susan Gilmour
Position	Professor Pediatrics, Director Pediatric Liver Transplant at University of Alberta, Edmonton, AB
Date	*25-10-2023*
[gJ	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	[gJ	☐	☐	☐
	☐	☐	D	☐

New or Updated Declaration for Clinician 18

Name	Vicky Ng
Position	Medical Director, Paediatric Liver Transplantation Transplant and Regenerative Medicine Centre, The Hospital for Sick Children, Toronto, ON
Date	*25-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10 000**	**$10,001 to 50 000**	**In Excess of $50.000**

None	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 19	
Name	Quais Mujawar
Position	Pediatric Gastroenterologist, Health Sciences Centre; Assistant Professor, University of Manitoba, Winnipeg, MB
Date	*25-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum		☐	☐	☐
Albireo/Ipsen (Medison)		☐	☐	☐

New or Updated Declaration for Clinician 20	
Name	Simone Kortbeek
Position	Pediatric Hepatologist, Alberta Children's Hospital, Pediatric Liver Centre, Calgary
Date	*25-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10 000**	**$10,001 to 50 000**	**In Excess of $50.000**
None	☐	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	Children's Hospital of Eastern Ontario (CHEO), Ottawa ONTARIO
Contact informationa	Name: Dr. Mohit Kehar, [redacted] Dr. Carolina Jimenez, [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No ☒

We, as a group of pediatric hepatologists at the Children's Hospital of Eastern Ontario (CHEO), wish to express our concern regarding the recent CADTH recommendation not to reimburse Maralixibat for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS). We understand the commitment to the highest level of evidence in healthcare decision-making; however, we believe there are compelling reasons to reconsider this recommendation. A critical aspect to consider is the potential impact of this recommendation on Canadian children with ALGS. If this recommendation is upheld, our Canadian children will be deprived of a treatment option that is available to patients in the United States and Europe. The intent to achieve the highest level of evidence, while commendable, may not be realistic in the context of rare diseases, particularly in the pediatric realm. In rare diseases, it is often challenging to accumulate a large patient population for clinical trials, and this can hinder the attainment of the highest level of evidence. We must recognize that the rare nature of ALGS makes it a unique challenge for the conduct of traditional, large-scale clinical trials. This recommendation may inadvertently discourage pharmaceutical companies from pursuing future trials for rare pediatric diseases, further limiting treatment options for these vulnerable patients.

First and foremost, we acknowledge that the CADTH Review Committee cited concerns related to the assessment of serum bile acid (sBA) levels, stating that they are not often evaluated due to high costs and logistical limitations. Furthermore, it was noted that there is a lack of evidence validating the correlation between sBA levels and improvement in pruritus (Page3). We appreciate the committee's diligence in evaluating the evidence; however, we believe it is essential to recognize that the evaluation of sBA levels may be challenging in clinical practice, but this does not negate the fact that they play a crucial role in understanding the pathophysiology of cholestatic liver diseases. Cholestatic levels of bile acids injure hepatocytes (Cai SY, Boyer JL. The role of bile acids in cholestatic liver injury. Ann Transl Med. 2021 Apr;9(8):737). We would like to emphasize that the measurement of Serum Bile Acids is a common and essential practice in the diagnosis of pediatric patients with cholestasis, including newborns. Another critical concern highlighted by the CADTH Review Committee was the enrichment trial design of the studies, which was cited as limiting the ability to assess the long-term efficacy and safety of Maralixibat. We acknowledge the importance of long-term data to assess the true impact of treatment, and we echo this concern. However, we must emphasize that, in rare diseases like ALGS, it is often challenging to conduct long-term studies due to limited patient populations. The committee also noted the unmet need for a therapy that can reduce pruritus frequency and severity, decrease patient and caregiver fatigue, and improve the quality of life for these patients and their families. Patients who participated in clinical trials shared

their experiences of itch relief and the positive impact Maralixibat had on their daily lives, which aligns with the clinical meaningfulness of treatment, as defined in the report. Our extensive discussions with colleagues in the medical field, participation in medical conferences, have all underscored the transformative impact of Maralixibat on patients ALGS. Maralixibat has provided newfound hope and relief from the relentless burden of pruritus and has significantly improved the overall well-being of these patients. We appreciate the rigorous evaluation conducted by the CADTH Review Committee, we urge you to reconsider your recommendation regarding Maralixibat for the treatment of Alagille syndrome and consider changing to reimburse with conditions. By not providing reimbursement, Canadian children with ALGS will be left at a disadvantage, and they can't access a treatment that has shown promise in alleviating their suffering.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	D
	No	IZJ

No, The recommendation made by the committee does not appear to reflect the stakeholder input that our organization, the Canadian Paediatric Hepatology Research Group (CPHRG, SIG of Canadian association for the study of liver) of which we both are part and Dr. Jimenez is the chair, provided to CADTH. As a collective of pediatric hepatologists from across Canada, we have offered expert recommendations regarding the use of Maralixibat in the context of Alagille syndrome (ALGS). Our input is rooted in the clinical expertise and experience of our group. Our goal, as pediatric hepatologists, is to ensure the best possible care and treatment for patients, particularly those with rare and complex conditions like ALGS. We believe that our input, which represents the consensus of pediatric hepatologists in Canada, would be considered in the decision-making process related to reimbursement. It is our sincere hope that CADTH will revisit this recommendation, taking into account the insights and expertise offered by the clinical community, and that they will give due consideration to the real-world experiences and needs of the patients we collectively strive to serve.

Clarity of the draft recommendation

3. **Are the reasons for the recommendation clearly stated?**	Yes	IZI
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	IZI

The concern raised by CDEC regarding Serum Bile Acids not being routinely tested due to high costs and logistical challenges is acknowledged (Page 3). However, we would like to emphasize that the measurement of Serum Bile Acids is a common and essential practice in the diagnosis and management of pediatric patients with cholestasis, including newborns. This diagnostic tool holds significant implications for accurate patient assessment and care planning.Furthermore, in the context of patients with Alagille syndrome, it is vital to recognize that these individuals are often managed at tertiary care centers, which are well-equipped to address the complex needs of patients with rare and challenging conditions. Tertiary care centers typically have the capability to perform Serum BA testing, either in-house or through established referral networks. Therefore, while logistical challenges may exist in some healthcare settings, it is essential to underscore that access to Serum BA testing is often readily available in the context of specialized care centers

	Yes	☐

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No
Not applicable, recommendation is not to reimburse	

a CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Mohit Kehar
Position	Pediatric Gastroenterologist and Hepatologist Assistant Professor Division of Pediatric Gastroenterology, Hepatology and Nutrition Children Hospital of Eastern Ontario, Ottawa
Date	*31-10-2023*

	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	181	☐	D	D
Medison	181	D	D	D

New or Updated Declaration for Clinician 2

Name	Carolina Jimenez MD, FCPSCR
Position	Associate Professor and Interim Chief, Division of Gastroenterology, Hepatology and Nutrition, Director, CHEO Liver Services
Date	*31-10-2023*
181	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	D	D	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	IWK Health Center, Dalhousie University, Department of Pediatrics 5850/5980 University Ave, Halifax NS
Contact informationa	Name: **Anthony Otley, MD, MSc,** Division Head Pediatric Gastroenterology [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No ☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

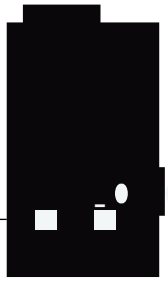
- Alagille is a RARE condition, most frequently diagnosed in pediatrics. An orphan disease. Pruritus is a major issue for these patients, sometimes the leading cause for liver transplantation.
    - Prior to maralixibat, all therapies used to manage pruritus had been studies in adults, with use in children without specific indication/study. Acknowledging that a large clinical trial is impracticable in this condition, we have a randomized controlled PEDIATRIC (withdrawal) study, that has evaluated this therapy for this specific patient population. As a clinician treating pediatric patients with this condition for over 25 years - and knowing the insufficient efficacy of the alternate therapies (often necessitating 2 or 3 medications used concurrently to get a degree of relief from pruritus), I cannot overstate how important access to this medication is for our patient population.
- I have used this medication with positive effect in Alagille syndrome with effect. Not in a controlled setting, but used in patients whose pruritus was suboptimally controlled on alternate agents (ursodeoxycholic acid, rifampin) but who experienced relief of pruritus on compassionate release maralixibat.
- Pages 9-13; Applying GRADE criteria to a rare condition, affecting pediatric patients, - one will NEVER be able to obtain high rating - too rare a condition to get a sufficiently large sample size in a RCT to not be downgraded. This is specifically disadvantaging this pediatric patient group. It is discriminating against this group.
    - Using the available (but, imperfect evidence - acknowledging limitations cited in CADTH review), as a clinician I keep coming back to fact that our alternative are multiple agents used which have undergone no pediatric study, and frequently result in imperfect treatment effect.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes No	☐ IZI

If not, what aspects are missing from the draft recommendation?

n/a I am a clinician (pediatric gastroenterologist), with 25+ years treating patients with cholestasis/pruritus secondary to Alagille syndrome. As above, see my concerns with the CADTH recommendation - , with all due respect, I don't think adequate attention was paid by the committee the patient or clinician group concerns.



Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	☐ IZI

If not, please provide details regarding the information that requires clarification.

As above, I am concerned about holding rare, 'orphan' pediatric conditions in which clinical studies have been conducted to the same level as GRADE criteria requires. The GRADE criteria are appropriate in adult studies and non-rare conditions, where large sample size sufficient to conduct studies deemed 'high quality/certainty are feasible. Holding therapies for orphan conditions like Alagille syndrome to this level, will fail to allow necessary therapies be available to patient populations like this. I see this as discriminatory.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☐ ☐

If not, please provide details regarding the information that requires clarification.

N/A

a CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
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  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. **Did you receive help from outside your clinician group to complete this submission?**	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. **Did you receive help from outside your clinician group to collect or analyze any information used in this submission?**	No	_
	Yes	○
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Anthony Otley
Position	Division Head Pediatric Gastroenterology, IWK Health Center, Dalhousie University, Department of Pediatrics
Date	*26-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	IZJ	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	Montreal Children's Hospital, McGill University Health Centre
Contact informationa	Name: Najma Ahmed MD, FRCPC, Pediatric Gastroenterologist
	[redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No ☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We follow patients with Alagille syndrome in the Division of Gastroenterology at the Montreal Children's Hospital, and see the burden of the cholestatic liver disease and pruritus on these patients and families. While our institution is in Quebec and the decision-making process in Quebec falls with INESSS, it is important that we advocate for access to this medication for our patients and children in Canada.
The options we currently have (anti-histamines, rifampicin, cholestyramine, ursodiol etc) are used off label and are suboptimal at controlling symptoms. Patients are usually on multiple medications and have persistent severe pruritus interfering with their QOL and their caregivers QOL. Marilixibat offers a first medication that is studied in Alagille syndrome and has a proven benefit in pruritus reduction and improvement in QOL as well as the potential of delaying or reducing the need for liver transplant in these patients.
Alagille syndrome is a rare disease and thus as pediatric gastroenterologists/hepatologists we each have small numbers of patients. The burden of pruritus on these children and their caregivers however is significant and is raised at every clinic visit. These children can have severe excoriations, sleep disturbance and the pruritus can interfere with activities of daily living including their ability to concentrate at school.

The decision to not approve this medication is taking away a proven option for treatment for Canadian children with Alagille syndrome. From the recent meeting of the North American Pediatric Gastroenterology Hepatology and Nutrition annual meeting in October 2023, marilixibat is now being used as standard care for children with this rare disease and has changed the lives of these patients.

With regards to the CADTH comment (page 3, paragraph 1) that serum bile acids are not relevant in clinical practice: bile acids can be sent routinely at our institution but have not been used regularly as it was not going to impact clinical management. With this medication, it will become clinically relevant to measure and follow bile acids. While the correlation of sBA and pruritus is not exact, this is the best biomarker that we have at this point in time and the correlation between these two variables has been alread documented.

With regards to safety, the ICONIC study[1,2] as well as other studies have demonstrated that this is a very safe medication with rare patients needing to discontinue the drug due to GI side effects. Also of note, the medications we currently use are all being used off label and without specific safety studies in Alagille syndrome.

The CADTH decision states that "no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence" and on page 14 that "Clinical trial evidence indicated that maralixibat may result in a clinically meaningful decrease in pruritis and may result in little to no difference in serious adverse events compared to placebo; however, there is evidentiary uncertainty concerning its safety and efficacy (particularly concerning its effect on long-term treatment outcomes and health-related quality of life). However, there are several publications including the ICONIC study that document the improvement in QOL.[1,3]

Furthermore, it is rare that we see trials in pediatric rare disease. The studies with marilixibat are sound and demonstrate the medication's efficacy and safety. In the setting of a rare disease such as Alagille syndrome, it would be impossible to generate further studies with adequate power in Canada to provide further evidence and as such, we would end up depriving Canadian children of a medication approved by the EMA and FDA and currently being used in the routine care of these patients. If CADTH's decision do not reimburse decision is upheld, it will be preventing children in Canada from an effective and safe medication to manage their pruritus, improve QOL and potentially delay the need for liver transplant.

1. Kamath et al. Maralixibat treatment response in ALGS is associated with improved health-related quality of life. J Peds 2022
2. Shneider et al. Impact of long-term administration of maralixibat on children with cholestasis secondary to ALGS. Hepatology Communications 2022
3. Gonzalez et al. Efficacy and treatment of marilixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomized phase 2 study. Lancet 2021.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? Yes ☐ / No ☒

If not, what aspects are missing from the draft recommendation?
We had previously not submitted input to CADTH.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated? Yes ☒ / No ☐

If not, please provide details regarding the information that requires clarification.
Yes but we do not agree with the recommendations as outlined above.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation? Yes ☒ / No ☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation? Yes ☒ / No ☐

Not applicable

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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.
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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1

Name	Dr. Najma Ahmed
Position	Pediatric Gastroenterologist Associate Professor, Pediatrics McGill University, Department of Pediatrics Residency Training Program Director, Pediatrics

Date	*01-11-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum		☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 2

Name	**Dr. Veronique Morinville**
Position	Pediatric Gastroenterologist Professor of Pediatrics McGill Universitv, Department of Pedaitrics
Date	*2023/10/31*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 **to 5,000**	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50 000**
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 3

Name	**Dr. Rilla Schneider**
Position	Pediatric Gastroenterologist Assistant Professor McGill University, Department of Pediatrics
Date	*2023/11/01*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None	☐	☐	☐	☐

New or Updated Declaration for Clinician 4

Name	Dr. Gael Kornitzer
Position	Pediatric Gastroenterologist Assistant Professor, Pediatrics McGill University, Department of Pediatrics Residency program director, Pediatric Gastroenteroloav
Date	*2023/11/01*
	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50 000**
None	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).
Organization	NASPGHAN (NORTH AMERICAN SOCIETY FOR PEIDATRIC GASTROENTEROLOGY HEPATOLOGY & NUTRITION. HEPATOLOGY COMMITTEE **MEMBERS OF THE GROUP AND AUTHORS OF FEEDBACK:** Saeed Mohammad Vanderbilt University Medical Center Taisa Kohut University of Miami, Miller School of Medicine Debora Kogan-Liberman, MD NYU Langone Mary Ayers UPMC Children's Hospital of Pittsburgh Amal Aqul, MD University of Texas Southwestern Medical Center in Dallas Phillipp Hartmann, MD, MAS University of California San Diego Julia Boster Children's Hospital Colorado Alisha Mavis MD Levine Children's Hospital *Catalina Jaramillo, MD,* MSc *Primary Children's Hospital* *Salt Lake City, UT* Janaina Nogueira Anderson MUSC Sarah Kemme, MD MSCS Monroe Carell Jr. Children's Hospital at Vanderbilt Charina Ramirez Institution: University of Texas Southwestern Medical Center, Dallas Catherine Chapin Lurie Children's Hospital Andrew Wehrman, MD Boston Children's Hospital Sarah Taylor MD Attendin Ph sician at Children's Colorado
Contact information[a]	Name: Saeed Mohammad MD [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes ☐ No IZI

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The Hepatology Committee of NASPGHAN representing the hepatology community in North America is disheartened by this draft recommendation and strongly disagrees with it. The recommendation will disadvantage Canadian children with Alagille syndrome (ALGS) and will unfairly restrict their access to a drug that has been approved globally for the treatment of cholestatic pruritus. It has tremendous proven symptomatic benefit on pruritus, quality of life, and has likely benefit in preventing the need for liver transplantation. Outside the clinical trials, our own clinical experience with this medication demonstrates its near miraculous effect on relieving pruritus, enabling children and parents to sleep, and function normally in school and work environments.

Page 3: Rationale for the Recommendation, Paragraph 1:
"CDEC noted that sBA is not of relevance in clinical practice since it is not often assessed due to high costs and logistical limitations, and that there is a lack of evidence validating the correlation between sBA levels and improvement in pruritis."

- We disagree with this statement. The primary reason why sBA have not been sent frequently in clinical practice, was because there were no therapies that targeted sBA. With the advent of medications such as maralixibat they have become part of routine clinical care amongst hepatologists in the United States. In some chronic liver diseases, ALGS being one, a patient can have elevated serum bile acids, severe pruritus and a normal bilirubin. In these patients this may be the only marker we have to assess the degree of cholestasis. Therefore, this statement may have been correct 5 years ago but in todays age it is false.
- We measure several biochemical markers of liver health at each clinic visit, and none of them on their own have a direct correlation with pruritus or severity of liver disease. It is well accepted that there is a close relationship between sBA and pruritus particularly in ALGS where sBA levels are very high. We believe that pruritus in cholestatic liver disease is caused by a factor that is present in, or derived from bile acids. Bilirubin levels were used previously but had even less of a correlation with pruritus. sBA are undisputedly the best available surrogate biochemical marker of pruritus available today.

Page 3: Rationale for the Recommendation, Paragraph 1:
"CDEC noted the enrichment trial design… thus limiting the ability to assess the long-term efficacy and safety of maralixibat."

- We now have almost 7 years of data in patients on maralixabat and therefore would have to disagree with this statement. Although the medication has been approved since 2021, the data from the clinical trials have been widely disseminated. As experts routinely caring for children with ALGS and using maralixibat, we can attest that this therapy has been transformative for children and their caregivers in terms of pruritus control. The safety profile is excellent with only isolated instances of maralixibat being discontinued for side effects.
- Our clinical experience is mirrored by a recently published manuscript "Impact of long-term administration of maralixibat on children with cholestasis secondary to ALGS" Shneider et al, Hepatology Communications 2022; which clearly describes the long-term efficacy in terms of pruritus, quality of life and safety on 57 children with ALGS pooled from four North American (including Canada) and UK studies. In their conclusions they state "Here we present data supporting the efficacy and durability of maralixibat treatment in children with ALGS and cholestatic pruritus in an international cohort. These investigators are part of an NIH-funded consortium, ChiLDReN, and independent of Mirum.

Page 4: Discussion Points, Paragraph 3:
"no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence."

- We disagree that the available evidence regarding the effects of maralixibat on quality of life are limited. The ICONIC data clearly show a positive effect. The changes in the PedsQL Multidimensional Fatigue Scale are not only significant, they are greater than in most studies. A recent study of CNS cancer survivors show PedsQL Fatigue score changes of eleven points after completing therapy. This demonstrates the dramatic change that is evidenced by patients taking Maralixibat. Secondly, the ICONIC quality of life data were anaylzed in further detail in a separate manuscript and published; "Maralixibat treatment response in ALGS is associated with improved health-related quality of life" Karnath et al, Journal of Pediatrics 2022. Finally, the manuscript referenced above, Shneider et al, Hep Comm 2022 also shows improvements in quality of life in a pooled cohort of 57 patients (separate to the ICONIC cohort).

Page *14: Critical Appraisal, Paragraph 1:*
"Concerns regarding the natural history comparison include the potential residual confounding, incomparability in disease severity, and the lack of sBA data available among patients in the GALA registry."

- We disagree with these concerns. The GALA registry is the largest and most comprehensive database of patients with ALGS and they have done their utmost to account for the issues listed above. Regarding the demographic and biochemical characteristics, the 2 groups were balanced for disease severity - we are unclear about the basis for the stated assessment that there was "incomparability in disease severity"
- Whilst there are certainly missing sBA data in GALA, we performed a sensitivity analysis for the availability of sBA levels and still found the same result and therefore believe this concern was adequately accounted for.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes ☐ No IZI

Page *7: Clinician Group Input, Paragraph 1:*

"None of the clinician group or clinical experts consulted by CADTH had declared experience with maralixibat"

- The NASPGHAN Hepatology committee has deep experience with maralixibat, and would be honored to provide the names of 15-20 clinical experts who could assist the committee with their decisions. It is important to note that pediatric hepatologists have greater experience than their adult collea ues as the disease is rimaril dia nosed in children

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes IZI No D

The reasons are clear but we strongly disagree as stated above. We request the opportunity to provide more detailed feedback to the committee as the page limitations of this document do not allow for it.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes IZI No D
If not, please provide details regarding the information that requires clarification.	Yes IZI

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐
If not, please provide details regarding the information that requires clarification.		

a CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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.
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  - Please add more tables as needed (copy and paste).
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A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Saeed Mohammad
Position	Hepatologist, Vanderbilt University Medical Center
Date	*31-10-2023*
	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	I2?J
Albireo	☐	☐	☐	I2?J

New or Updated Declaration for Clinician 2	
Name	Taisa Kohut
Position	Hepatologist, University of Miami, Miller School of Medicine
Date	*31-10-2023*
I2?J	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	I2?J
Albireo	☐	☐	☐	I2?J

New or Updated Declaration for Clinician 3	
Name	Debora Kogan-Liberman, MD
Position	Hepatologist, NYU Langone
Date	*31-10-2023*
I2?J	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	I2?J
Albireo	☐	☐	☐	I2?J

New or Updated Declaration for Clinician 4	
Name	Amal Aqul, MD
Position	Hepatologist, University of Texas Southwestern Medical Center in Dallas
Date	*31-10-2023*
	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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50 000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 5	
Name	Mary Ayers
Position	Hepatologist, UPMC Children's Hospital of Pittsburgh
Date	*31-10-2023*
	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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 6	
Name	Phillipp Hartmann, MD, MAS
Position	Hepatologist, University of California San Diego
Date	*31-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10.000	$10,001 to 50 000	In Excess of $50 000
Mirum	☐	☐	☐	1:83
Albireo	☐	☐	☐	1:83

New or Updated Declaration for Clinician 7

Name	Julia Boster
Position	Hepatologist, Children's Hospital Colorado
Date	*31-10-2023*

1:83 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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum	☐	☐	☐	1:83
Albireo	☐	☐	☐	1:83

New or Updated Declaration for Clinician 8

Name	Alisha Mavis MD
Position	Hepatologist, Levine Children's Hospital
Date	*31-10-2023*

1:83 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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum	☐	☐	☐	1:83
Albireo	☐	☐	☐	1:83

New or Updated Declaration f[redacted]

Name	*Catalina Jaramillo, MD,* MSc

Position	Hepatologist, *Primary Children's Hospital, Salt Lake City, UT*
Date	*31-10-2023*

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.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 10

Name	Janaina Nogueira Anderson
Position	Hepatologist, MUSC (Medical University South Carolina)
Date	***31-10-2023***

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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	D	
Albireo	☐	D	☐	

New or Updated Declaration for Clinician 11

Name	Sarah Kemme, MD MSCS
Position	Hepatologist, Monroe Carell Jr. Children's Hospital at Vanderbilt
Date	*31-10-2023*

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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	Excess of $50,000

Mirum	☐	☐	☐
Albireo	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	Charina Ramirez
Position	Hepatologist, Institution: University of Texas Southwestern Medical Center, Dallas
Date	*31-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 13	
Name	Catherine Chapin
Position	Hepatologist, Lurie Children's Hospital
Date	*31-10-2023*
	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 14	
Name	Andrew Wehrman, MD
Position	Hepatologist, Boston Children's Hospital
Date	*31-10-2023*
	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

New or Updated Declaration for Clinician 15	
Name	Sarah Taylor MD
Position	Hepatologist, Attending Physician at Children's Colorado
Date	*31-10-2023*
	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum	☐	☐	☐	
Albireo	☐	☐	☐	

Cut/paste to add additional Declarations for each person in authorship

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	Pacific Gastroenterology Associates, Vancouver, BC, V6Z 2K5
Contact informationa	Name: Dr. Hin Hin Ko, Hepatologist [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

I am a Clinical Associate Professor of Gastroenterology and Hepatology at the University of British Columbia and have been in practice for over 10 years. I have looked after patients with Alagille syndrome and fully understands the significant impact of cholestatic pruritus, a debilitating symptom, on the quality of life in this population and their families. Although currently there are medications used for cholestasis-related pruritus (i.e. ursodeoxycholic acid, cholestyramine, rifampin, sertraline and naltrexone), none of them when used alone or even in combination have led to major improvement in pruritus.

It is difficult to conduct long-term conventional large randomized clinical trials in rare disease, such as Alagille syndrome. Maralixibat, an ileal bile acid transporter blocker, had been shown to reduce bile acids and improve itchy severity (Itch-reported Outcome ItchRo) and improved quality of life (Qol) and Multidimensional Fatigue Scale based on the recent systematic review and meta-analysis and the use of multicenter prospective longitudinal database by the Childhood Liver Disease Research Network (ChiLDRen). Before maralixibat, there have been no approved treatments to date for cholestatic pruritus in Alagille syndrome and children ultimately require major surgical intervention, such as liver transplantation, for refractory pruritus. In 2021, maralixibat was approved by FDA as a treatment of cholestatic pruritus in patients with Alagille syndrome . Approving maralixibat in Canada would signify a meaningful, and positive shift in treatment paradigm for Alagille syndrome in Canada and provides tremendous hope for the young patients (and their families) who have been living with pruritus for a long time.

As clinicians, we sincerely hoped that CADTH would re-consider the decision by approving maralixibat for reimbursement with conditions.

Additional References:
Muntaha HS, Munit M, Sajid SH, et al. Ileal Bile Acid Transporter Blocker for Cholestatic Liver Disease in Pediatric patients with Alagille Syndrome: A Systematic Review of Meta Analysis. J Clin Med. 2002; Dec 11(24): 7526.

Shneider B, Karnath BM, Magee JC, et al. Use of funded multicentre prospective longitudinal databases to inform clinical trials in rare diseases - Examination of cholestatic liver disease in Alagille syndrome. Hepatol Commun. 2002 Aug; 6(8); 1910-21.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes No	D [81

We acknowledge that COED would like to see more data in a larger randomized controlled trial for a longer period, However, such a study would be difficult to conduct in rare disease such as Alagille syndrome. Based on the current information, among all therapeutic agents available for cholestatic pruritus in Alagille syndrome, maralixibat has shown to improve itch and improve quality of life and hence we hope that CADTH would consider the decision.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes No	[81 ☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	[81 ☐

If not, please provide details regarding the information that requires clarification.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☐ ☐

Not applicable

a CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Hin Hin Ko
Position	Clinical Associate Professor, Hepatologist
Date	*31-10-2023*

	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	181	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	For the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization	Autoimmune and Rare Liver Disease Clinical Programme Toronto Centre for Liver Disease, Toronto General Hos ital
Contact informationa	Name: Dr Gideon Hirschfield, Director Autoimmune and Rare Liver Disease Programme, Lily and Terry Horner Chair in Autoimmune Liver Disease Research, [redacted] Name: Dr Aliya Gulamhusein, Professorship in PSC,
	[redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No

We are the largest adult ambulatory liver disease programme in Canada, and likely the largest programme in North America. As a result of this, and aligned with our academic mission, we manage a unique in size autoimmune and rare liver disease cohort of patients, including transitioning care from paediatricians. Alagille syndrome is a **very** rare but impactful cholestatic liver disease; we see adult patients with this disease and manage probably under 10 patients who have not needed to have a liver transplant in childhood. For this very small, but nevertheless important, group of patients there is clearly a need for new therapy with a focus on quality of life (itch) as well as disease progression. It is remarkable at all that there is new drug discovery for these patients given the disease is rare and as a result prospective clinical data on patient impact challenging to assemble. Already health care barriers in Canada (rare disease, large geographic territory, few specialist programmes) mean patients struggle to get access to expert care, let alone access to research protocols. That said it is notable that there is a pan-industry (at least three different sponsors to my knowledge) working on IBAT inhibitors to treat pruritus from cholestatic liver disease. Livmarli is one such drug that has clearly demonstrated appropriate efficacy in clinical trials, that are very hard to conduct, but the results of which are demonstrably positive.

As clinicians our focus is on quality of life first (itch) and then on disease modification. Surrogates of disease activity (bile acids) are not used routinely as they are not available in a widespread manner; that said there is a recognition that mechanistically bile acids are key aspects of cholestatic pruritus, and that the enterohepatic circulation of bile acids is key physiologically and pathophysiologically. Whilst there is a correlation between bile acid values and outcomes (clinical and symptoms), because until now there has been no clinical treatment choices, we do not measure bile acids regularly, and as such it is not possible to have ideal datasets for evaluation. Not measuring bile acids is appropriate current clinical practice ('choosing wisely') but should not then be used as a reason to impair access to new therapies, that by the nature of the mechanism of action, should interrogate the impact of treatment on bile acids, and appropriately aligned with the accepted concept that an improvement in symptoms will parallel bile acid reduction.

This means when evaluating a new therapy, this needs to be recognised as there will be an inevitable gap between the science of cholestatic pruritus (bile acid science, IBATs, C4 activity, enterohepatic circulation) and the practice (qualitative assessment, patient centred care). CADTH therefore have reached a surprising decision to not conclude based on the data available to 'Reimburse with Conditions'. It appears on my review of the documentation that CDEC is applying an impossibly high bar for evidence evaluation, that no rare disease patient population could realistically in Canada be expected to meet. This evaluation is a direct barrier to a small number of patients in Canada receiving therapy and is evaluating the impact of a new therapy in a way that an ultra-rare liver disease could never meet. Given the importance everyone places on patient quality of life, this decision must be appealed. I would therefore challenge and support a re-evaluation of some of the interpretations made, asking that the assessment is grounded in the ultra-rare nature of this disease, how practice is for Canadian Alagille patients, and what one can reasonably expect of data evaluation at this time.

Specific areas of concern include:

Page 3: Rationale for the Recommendation, Paragraph 1:

"CDEC noted that sBA is not of relevance in clinical practice since it is not often assessed *due to high* costs *and logistical limitations, and that there is a lack of evidence validating the correlation between sBA levels and improvement in pruritis."*

"CDEC noted the enrichment trial design... thus limiting the ability to assess *the long-term efficacy and safety of maralixibat."*

Page 3: Rationale for the Recommendation, Paragraph 2:

"need for...reduced the frequency and severity of pruritis, reduced patient and caregiver fatigue. CDEC was unable to determine whether maralixibat would meet any of these needs given the concerns with evidence previously described."

Page 4: Discussion Points, Paragraph 2:

"CDEC noted that it is unclear the extent to which sBA levels may be associated with pruritis in patients with cholestatic liver diseases.

Page 4: Discussion Points, Paragraph 3:

"no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence."

All these points are positioning the evidence level for this ultra-rare disease at a point that is unattainable, and not aligned with the totality of the current data (trial and observational), the field of cholestatic pruritus generally, and the clinician/patient experience in the real world. Additionally, whilst I am not a paediatrician and have not taken part in the development of this drug, as a clinical programme of excellence, it is relevant to recognise our involvement in adult trials of cholestatic pruritus using agents from the same class. I believe this provides important corollary evidence of the importance of bile acids in pruritus, and why the data for this ultra-rare disease should be interpreted favourably.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? Yes ☐ No

If not, what aspects are missing from the draft recommendation?
I understand that the Canadian Association for the Study of the Liver who is at a national level, a key stakeholder, has raised similar points to those we are raising now.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	

If not, please provide details regarding the information that requires clarification.

The assessment is not taking account appropriately of how ultra-rare Alagille's is, how symptoms are so important, and how it cannot be realistic to set an evidence threshold so high. The approach appears to raise a barrier to symptom therapy for ultra-rare biliary disease in Canada.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	

If not, please provide details regarding the information that requires clarification.

See above.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	

If not, please provide details regarding the information that requires clarification.

It is unclear to us why a conditional approval cannot be given; we are not reimbursement experts, and our comments are not informed by any knowledge of proposed cost. But we are experts in management of common and rare cholestatic liver disease. This new therapy, as others in the same class are likely to be in the future, offers significant hope for patients, and beyond hope there is more than sufficient evidence to support use in Canada for the small number of Alagille's' patients, with ongoing evaluation of impact.

a CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
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  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	_
	Yes	O
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. **Were** conflict of interest declarations provided in clinician group input that was **submitted at the outset of the CADTH review and have those declarations remained unchanaed? If no, please complete section C below.**	No	
	Yes	D
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Gideon Hirschfield MB BChir PhD FRCP (Lon)
Position	Director, Autoimmune Liver Disease Programme, Toronto Centre for Liver Disease, Lily and Terry Horner Chair in Autoimmune Liver Disease Research, University Health Network
Date	*25-10-2023*

	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum- clinical trial site for adult PSC *pruritus study*	D	D	1:8:1	☐
Albireo- advisory board	1:8:1	☐	☐	D
GSK - *clinical trial site for adult PBC pruritus study*	D	D	1:8:1	D

New or Updated Declaration for Clinician 2	
Name	Dr. Aliya Gulamhusein, Hepatologist
Position	Assistant Professor of Medicine, University of Toronto Clinician Investigator, University Health Network
Date	*25-10-2023*
1:8:1	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.

Conflict of Interest Declaration

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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
None	D	☐	D	D

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0780
Name of the drug and Indication(s)	Maralixibat (Livmarli) For the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS)
Organization Providing Feedback	FWG

1. Recommendation revisions

Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation

Request for Reconsideration	**Major revisions: A** change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are reauested	X
	No requested revisions	☐

2. Change in recommendation category or conditions

Complete this section if major or minor revisions are requested

Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation

a) Recommendation rationale

Please provide details regarding the information that requires clarification.

Clarification is required to better explain the rationale for the recommendation given the results presented in the Clinical Evidence section of the report for change in sBA and ItchRO severity score.

b) Reimbursement conditions and related reasons

Please provide details regarding the information that requires clarification.

c) Implementation guidance

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions

1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.

Support strategy

3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	LIVMARLI (maralixibat)
Indication(s)	LIVMARLI is indicated for the treatment of cholestatic pruritus in patients with Alagille Syndrome (ALGS).
Organization	Canadian PBC Society
Contact information	Name: Gail Wright [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No cgi

I am President of the Canadian PBC Society, a registered Canadian Charity supporting patients with Primary Biliary Cholangitis, a rare autoimmune liver disease. We are keenly interested in this file, because like ALGS patients, PBC patients suffer from debilitating cholestatic pruritus. We are anxiously awaiting results from three clinical trials that are currently underway for cholestatic pruritus in PBC: Linerixibat, Volixibat and EP547. The Canadian PBC Society was excited to learn of Health Canada's approval of the first treatment for cholestatic pruritus, for ALGS patients; however, we are extremely disappointed in the "DO NOT REIMBURSE" recommendation and respectfully request that you reconsider the following:

CADTH Draft Recommendation - *Ethical Considerations pages 14-15:*

'There is evidentiary uncertainty concerning its safety and efficacy... (particularly concerning its effect on long-term treatment outcomes and health-related quality of life) which limits the assessment *of clinical benefits and harms associated with its use"*

In Canada, patients trust Health Canada to approve drugs that they deem to be safe and effective based on clinical trials and scientific evidence. Because Health Canada has approved maralixibat, patients believe that it meets the safety and efficacy criteria. However, the draft recommendation statement above puts into question Health Canada's determination. This is contradictory and confusing to patients.

Health Canada understands the reality that clinical trial sizes will be small for rare and ultra-rare diseases, such as PBC and ALGS, and to fully understand the long-term impact of these therapies depends on innovative follow-up and monitoring programs. As such, there needs to be a balance between achieving absolute certainty and the urgent need to get new treatments to underserved patients. Furthermore, by denying Canadian patients access to approved therapies, companies are discouraged from attempting to deliver new therapies to Canadian patients. We aspire to improve the quantity and quality of life for all rare disease patients, and we advocate for equal access to approved treatments that can help improve their lives.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes No	☐

Concerns about short- and long-term safety and efficacy are disproportionally weighted in the recommendation, which discounts the magnitude of the impact of cholestatic pruritus on ALGS patients and their families. We believe, the statements below, supported by the detailed patient and clinician accounts of the lived experience of ALGS patients and their families, are compelling and justify a recommendation to REIMBURSE.

CADTH Draft Recommendation - *Ethical Considerations pages 14 -15:*
'There is a significant unmet need for an effective treatment for cholestatic pruritus in ALGS due to its devasting impacts on patients and their families; the limited efficacy of and adverse effects associated with currently available off-label therapies; and the invasive life-altering nature of surgical treatment alternatives such as liver transplantation."

CADTH Draft Recommendation - *Patient Input page 5:*
"*...theitchiness (pruritus) is the most bothersome symptom...[it] interrupts sleep making those affected fatigued, anxious, depressed, irritable and worried."*

"Patients who have taken maralixibat during clinical trials said that their itchiness has been resolved with minor side effects, such as upset stomach, diarrhea, could become more of themselves, engage in normal day-to-day activities and their households were also positively changed"

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes No	☐ ☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	☐ ☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☐ ☐
NA		

a CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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.
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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information

Name	*Gail Wri ht*
Position	*President, Canadian PBC Socie*
Date	*1025/2023*

IZI 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.

B. Assistance with Providing Feedback

1. **Did you receive help from outside your patient group to complete your feedback?** No / Yes ☐

If yes, please detail the help and who provided it.

2. **Did you receive help from outside your patient group to collect or analyze any information used in your feedback?** No / Yes IZI ☐

If yes, please detail the help and who provided it.

C. Previously Disclosed Conflict of Interest

1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section **D** below. No IZI / Yes ☐

D. New or Updated Conflict of Interest Declaration

3. 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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum Pharmaceuticals	☐	IZI	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).
Organization	PFIC Advocacy and Resource Network, Inc
Contact informationa	Name: Walter Perez, President [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No ☒

Thank you for allowing our organization, the PFIC Network, an opportunity to comment on the initial decision for the guidance on using Maralixibat for cholestatic pruritis in patients ALGS.

The cholestatic pruritis experienced in PFIC is the same as in ALGS. As the only patient led organization that represents PFIC patients and families, including those in Canada, we are grateful for the opportunity to respond to the draft CADTH recommendation for maralixibat.

Often the hallmark feature of this disorder is severe and debilitating pruritus (itching). While your committee has made an initial decision not to recommend reimbursement for Maralixibat in Canada, we understand the importance of this opportunity, and want to share with you another side of PFIC and the promise that Maralixibat brings to PFIC patients and their families.

Because the age of diagnosis and onset of symptoms is so young, ALGS and PFIC become diseases that affect not only the individual, but also every member in the family. I can tell you firsthand, as a father of a child with PFIC, this disease will wind its way into every part of a family's life. The relentless itch makes living a "normal" life nearly impossible. Sleep disturbances, treating damaged or broken skin, and the emotional toll of trying to comfort a child desperately wanting to stop itching.

It is more than just an itch-families lose jobs, children can't attend school, parents feel helpless, siblings neglected-all because of itch. The itch becomes so intrusive that families are left looking for anything to help their child feel relief. Excerpts from testimonials of families:

> *The pruritus* was *increasing and no balms for atopic skin helped, and no allergy medications and sedatives. I kept her nails short. I think that only someone with a similar disease will understand* us. *The itching caused her to sleep for 15 minutes and wake up crying and scratching constantly. I* was *taking her hands away because she* was *scratched to blood, but she* was *still doing the* same. *It* was *like a fight. At night, when it* was *dark, I knew she* was *scratching because I could smell her blood. Nobody wanted to care for her during the day because they were afraid of her scratching attacks. Besides, she just wanted to come over to me. This tiredness on our part* was so *great that I thought that I would commit suicide because in our house there* was *only crying and nerves between* us *in the household. Fatigue, lack of sleep,* stress.
>
> *The nights were the worst. I only remember a terrible cry, often screaming, scratching herself to the blood, torn ears, and a nose with* scars so *dee . Due to the lack of slee , she* was

always angry and irritable. I couldn't watch how much my beloved child was suffering ... This itch cannot be compared to anything else.

Lena kept scratching herself to the point of blood. She woke up crying, she could not sleep because the itching of the skin was so increasing that she could not stand the pain. More than once I heard from people, family friends, why is she so scratched?

Life with Stas' itching was extremely exhausting for our whole family, there was no way to help him, nothing brought relief. We put gloves on him, we held hands so that he wouldn't scratch himself, which made him cry even more. He couldn't sleep because after a few hours he was awakened by itching. It is so strong that even in publications you can read that in extreme cases it can cause suicide.

One of the most challenging things we have had to endure is watching him self harm while scratching to try and relieve himself from the intense sensation of pruritis.

Here are testimonials on how pruritus can impact the whole family:

My daughter has PFIC 2, we watched her as a newborn and for the first year of her life suffer a non-stop, torturous, painful, endless horrendous itch that covered her entire body. She cried non-stop, slept for only 15 minutes at a time, she was never still and tried to scratch any way she could, her skin was full of scabs. she would only get three to four hours of broken sleep every 24 hours. My then, two-year-old son suffered terribly with parents that barely slept and a new sibling that was writhing in pain. The itch was so bad that my intense fear of transplant was overtaken by the need to get rid of this itch, it was destroying her life and that of my families. I felt sick to my stomach because the research and statistics on liver transplant are not so good, going through a transplant is a horrific experience in itself and even if we had a transplant, she had to endure months or perhaps years of this unbearable itch while she waited for an appropriate liver to become available.

My daughter has PFIC 2 and is awake all through the night, crying in pain due to the itching. Her 4 year old brother has nightmares due to her constant cries and her pain. He does not sleep well and acts out at school. His classmates tease him because his sister has scabs all over her body. He got in a fight at school as he was defending her. One day, he told me that he wanted to go live with his grandfather, so that he does not need to hear Eva's cries.

Families even **chose** transplant—risking their child's life—to try for a chance to help their child stop itching. Can you imagine? Choosing an expensive, devastating, risky, intrusive, life-changing surgery in order to help your child not to itch.

Sharon, shares her family's experience with a decision of surgical interventions:

*The current treatment is not a treatment at all. Kids end up taking various medications that may or may not reduce their symptoms, and often come with a lot of other detrimental side effects. When these don't work or when they stop working, the next and only other option is to undergo invasive surgical interventions. My child has had 5 surgeries to manage their disease; two of them were due to life threatening complications of previous surgeries. I find it reprehensible that access to a medicine that could treat pruritus and stop disease progression would be withheld in favor of risky surgical intervention…. **The cost of "managing" PFIC with the current options is extraordinary**. For example, our family has spent over 6 months of the last 12 months in the hospital due to transplant and transplant related complications. Not only has that had significant impacts on the healthcare system, but it has also been*

detrimental to our child's quality of life and development. For our family, it has meant loss of jobs, reliance on social/governmental support programs, etc.

These are the options we are left with. But it doesn't have to stay that way. Maralixibat is the first time patients and families have had a glimpse for safe, life-changing, non-invasive, non-surgical hope.

From a PFIC caregiver, about her son, Armando, and the hope that came with Maralixibat:

> *"PFIC is a life altering, painful, traumatic disease that has left us feeling hopeless and desperate for treatment. We have a 6 yr old son who has been diagnosed with PFIC 2. The pruritis that he has experienced has affected his sleeping, his eating, his mental health and his quality of life. The pruritis was so intense that he was physically unable to sleep and physically unable to eat the majority of the time. This disease has robbed him of a joyous childhood. One of the most challenging things we have had to endure is watching him self harm while scratching to try and relieve himself from the intense sensation of pruritis. This disease has not only effected our boy but it has rippled into effecting our whole family. The symptoms of PFIC affected how he played with his siblings, how we as a family used our time and how we used our finances. When our son started taking Maralixibat as part of a clinical trial his entire life changed almost immediately. He no longer scratches at all. He is able to sleep, play with his siblings, and he eats well and is gaining weight again. He is even flourishing at school. We finally got to meet who our boy truly is.* ***In short, it has saved our son and our family from a most dismal future and greatly reduces the prospect of overutilizing our national health resources.*** *We believe there is a desperate and urgent need for new treatments to be available. Current medical options offer little to no symptom relief. New treatments would significantly increase the quality of life for those affected by PFIC. New treatment options would allow families not to have to put their child's life at risk by going through a liver transplant. If access to new treatments is denied it will leave families hopeless and devastated." Alexandra, parent to 6 year old Armando*

With this submission, we earnestly request that your committee reconsider your decision for reimbursement. Maralixibat gives patients an opportunity to feel relief from this debilitating itch that increases their chance of survival (compared to a liver transplant, the only other proven intervention to remove itch).

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes ☐ No ☒
We do not agree, for the reasons outlined above regarding severe and debilitating nature of pruritis	

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes ☒ No ☐
If not, please provide details regarding the information that requires clarification.	
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes ☒ No ☐
If not, please provide details regarding the information that requires clarification.	
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes ☐ No ☐
Not applicable	

a CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CAOTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information

Name	*Walter Perez*
Position	*e i t, voca ou c et , nc*
Date	*0*

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.

B. Assistance with Providing Feedback

1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐

If yes, please detail the help and who provided it.

2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	
	Yes	☐

If yes, please detail the help and who provided it.

C. Previously Disclosed Conflict of Interest

1. **Were** conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section **D** below.	No	-Yes--+--☐

D. New or Updated Conflict of Interest Declaration

3. 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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10 000**	**$10,001 to 50 000**	**In Excess of $50.000**
Mirum Pharmaceuticals	☐	☐	☐	
Albireo Pharmaceuticals	☐	☐	☐	

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Instructions for Stakeholders

This template is for eligible stakeholders to provide feedback and comments on draft reimbursement recommendations. Draft recommendations are available for feedback for 10 business days.

CADTH will only consider feedback received from eligible stakeholders, including the sponsor, patient groups, clinician groups, and the participating drug programs. Individuals interested in providing feedback should contact the relevant patient and clinician organizations. This template may also be used by eligible industry stakeholders to provide feedback on draft recommendations from the non-sponsored review process (i.e., any current or future Drug Identification Number [DIN] holders for the drug under review).

All submitted feedback must be disclosable and will be posted on the CADTH website.

If you have questions, please email requests@cadth.ca with the complete details of your question(s).

Before Completing the Template:

Please review the following documents to ensure an understanding of CADTH's procedures:

- Procedures for CADTH Reimbursement Reviews

Completing the Template:

Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph).

Comments should be restricted to the content of the draft recommendation.

Feedback must be based on the information that was considered by the expert committee in making the draft recommendation. No new evidence will be considered at this part of the review process.

Feedback must not exceed 3 pages in length, using a minimum 11-point font on 8.5″ by 11″ paper. If comments exceed 3 pages, the feedback will not be accepted by CADTH. References may be provided separately; however, these cannot be related to new evidence.

Patient groups must complete Appendix 1.

Filing the Completed Template:

The feedback must be provided in Microsoft Word format by using the *Submit* link next to the drug on the Open Calls page. In order to ensure fairness in CADTH's procedures, all stakeholder feedback must be received by the deadline posted on the CADTH website.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).
Organization	Canadian Liver Foundation
Contact informationa	Anisha Vijh
	[redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No cgi

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Page 3: Rationale for the Recommendation, Paragraph 2: "need for...reduced the frequency and severity of pruritis, reduced patient and caregiver fatigue. COEC was unable to determine whether maralixibat would meet any of these needs given the concerns with evidence previously described."
Page 4: Discussion Points, Paragraph 3: "no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence."

The Canadian Liver Foundation does not agree with the committee's recommendation. We believe that there is a strong need for patients to have access to available treatment. Patients and family members that contact the CLF have expressed their need to have access to effective treatment to manage the pruritis that patients live with along with management of fatigue among parents and caregivers.

When asking parents and/or caregiver of loved one's living with Alagille syndrome, respondents indicated how an Alagille syndrome diagnosis has severely impacted the lives of their loved ones and affected their day-to-day activities, while adding physical and emotional stressors and worries:

"We struggled from day one with our son, with failure to thrive, not eating, not sleeping. We live in a very rural community and the access to any type of specialist was not there. No one really knew what was going on with him. He would scratch his entire body raw all the time. For the first 6 years of life, we never had the option of sleeping through the night because he was always up." - Parent

"Oh gosh, it became our entire life, as a parenting team, when you have a medically fragile kid. We went from husband and wife and parents to co-case managers. You go into survival mode, and it just becomes your entire life - you're changing bloody sheets constantly. When they have that internal itch that they can't scratch, it's like watching your kid's body torture themselves and there's nothing you can do, it's all consuming and it's just awful. With medications, we can look at nutrition and other things special needs parents might deal with, but it's not as all-consuming as when the itch is there." - Parent

"Sleeplessness - the kids, siblings, the parents. It really affects the whole family." - Parent

"There was no sleep. We try all night to help in whatever way, while watching your child suffer. It was almost traumatic because you can't control any of it. All you can do is help in the best way you can, but that almost always failed." - Parent

The interview respondents expressed the improvements in their overall quality of life once they began treatment and limited challenges with obtaining the treatment:

"Before maralixibat, the itch was just unbearable for him. He was so unhappy. We have since been on maralixibat for 2 years now. He is turning into a man, he is eating better, the biggest thing is that there is no itch, at all. The biggest impact is that we see this incredible young man, he has such a fun sense of humor that we have never seen before. None of this would have happened if we were not on this medication. Is it a miracle drug? Yeah." - Parent

"The treatment - you can't even compare the treatments, none of the other ones worked, and the maralixibat worked, we tried every other therapy and treatment, we tried everything we could, and nothing helped." - Parent

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? Yes ☐ No

Page 4: Patient Input, Paragraph 1: "... want a new therapy that can provide significant relief of itchiness with long-term effects without high risks such as liver transplant and immunosuppression. Patients who have taken maralixibat during clinical trials said that their itchiness has been resolved with minor side effects, such as upset stomach and diarrhea, could become more of themselves, engage in normal day-to-day activities, and their households were also positively changed."

This input does not seem to be reflected/considered in the CADTH recommendation, considering how life changing it has been for the many Canadian patients that have accessed maralixibat through clinical trial or SAP program, etc).

The Canadian Liver Foundation believes that liver disease patients, their caregivers and health care providers should have access to the most effective treatment options regardless of geographical location, financial status, treatment status or disease severity in order to ensure the best possible outcomes. The hope is that access to maralixibat will mean that patients and caregivers will have improved and increased access to treatment. However, if accessing maralixibat is not seamlessly and readily available as part of various provincial reimbursement programs, then patients will not have access to these treatments. We therefore strongly support and urge that a positive funding recommendation be issued for maralixibat for the treatment of cholestatic pruritis in patients with Alagille syndrome. We believe a positive funding recommendation aligns well with the identified patient need for a new, effective, easily administered treatment option that is capable of maintaining a high quality of life and durable response.

"Today my son (Chord) is growing, sleeping, eating, and living. He has been using Livmarli since Feb 2021 and the relief from itch has changed all our lives. Chord takes music class, animation lessons, dance training and joined a sledge hockey team. He sleeps more than 2 hours at a time during the night and rarely misses a day of school. Chord is joyful. He smiles. Our family has a future that isn't shadowed with constant fear and distress. Since learning of this decision our family has been in shambles. We feel powerless and are consumed with fear. Not worry, not sadness, not distress but complete and utter fear. No human should be left to suffer when there is a treatment available. My son is not a patient, a number or a dollar sign. He is a human being- please do not take his life away." - Parent

"I hesitate to use life-changing because it's so cliche, but it completely changed him. It was the first time we got to see his personality and felt like we got to meet our child for the first time. Before the maralixibat, he just cried, and scratched, and we were up every 2 hours, he was being tortured by his body all the time. He began to eat, he slept, he could play, he could think, it took the itch completely away." - Parent

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes No	cgi D
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	cgi D
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☐ D
N/A		

a CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information

Name	*Anisha Vi"h*
Position	*Health Promotion Pro ram Coordinator*
Date	*31-10-2023*
IZI	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.

B. Assistance with Providing Feedback

1. Did you receive help from outside your patient group to complete your feedback?	No Yes	 ☐

If yes, please detail the help and who provided it.

2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No Yes	IZI ☐

If yes, please detail the help and who provided it.

C. Previously Disclosed Conflict of Interest

1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section **D** below.	No	IZI ☐

D. New or Updated Conflict of Interest Declaration

3. 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.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
NIA	D	D	☐	D
NIA	D	☐	☐	D

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	For the treatment of cholestatic pruritus in patients with Alagille Syndrome (ALGS)
Organization	Alagille Syndrome Alliance
Contact informationa	Name: Roberta Smith and Cher Bork

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	**X**

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Our main job as the leading global resource and advocate for Alagille patients around the world is to elevate their voice in any setting necessa1y. We disagree with many points in this recommendation, specifically with your acknowledgements of the physical, psychosocial, and financial impacts of pnuitus on patients and families while minimalizing the many patient perspectives oliginally submitted. We also disagree that the heavy voice given to the CADTH clinical group who offered insights was based, admittedly, on no expelience whatsoever with treating cholestatic pmritus with Livmarli. Yet, top Alagille syndrome expe1t clinicians reside and practice right in Canada and were overlooked by the CADTH committee. With the utmost respect, we want to take this opportunitysolely to share real-life reaction and patient perspective directly from the TRUE EXPERTS in the Alagille syndrome space, the patients and caregivers. We feel their reaction to yom recommendation, including individuals botl1in Canada and outside of Canada, spe.ak strongly in opposition to your recommendation to not reimburse. As well, due to a lack of available evidence no conclusion could be reached regarding the effects of maralixibat on quality oflife. We stand together as a community, and with 75+ testimonies, quotes, and opinions originally provided from Alagille patients and families, we hope you see the breadth and depth of the real-world reality tliat seems minimized in your recommendation. Shockingly, a lack of "real-world" experience was repeated tluoughout the recommendation and for that reason, we have decided to provide the "real-world" more succinctly by creating an experience for you to witness the real-world of cholestatic pnuitus for Alagille patients. We ask you to watch tllis video and reconsider yom recommendation for Alagille families suffering from pnu'itt1s in Canada. There are no other effective treatments, which you confinn in your recommendation, and patients waiting without this diug until they can get transplanted is not a sustainable quality of life reality. Livmarli is specifically effective in relieving the physical and emotional results of pmritus which over 75 patients and families have conveyed. Moreover, Livmarli is helping patients and families thrive. They have seen, demonstrated, and live daily the proof that this diug is effective both sho1t term

and long term. Their positive life-changing results stemming from the use of thismug, accompanied by their heightened fears and desperation that it could be taken away, speak for themselves.

CLICK HERE for Patient Perspective: https://vimeo.com/880193077/5816e5db51?share=copy

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	**X**

If not, what aspects are missing from the draft recommendation?

Although we feel it was considered, we do not feel our input which piimarily contains patient perspective, was given the weight in the recommendation it deserves. Please see Question #1.

Additional Written Patient and Family testimonies:
https://docs.google.com/document/d/16VwbCpypLolq0B9zg2iSi..BG8N7ziDO45lgHcDLoioAk/edit?usp=sharing

Some highlighted testimonies from this link, above:

Chord, Ontario, Canada - "For your consideration, I have been a medical mom since Jan 6, 2012. My sweet 2lbs baby has been fighting his body from the moment he was born. Scans, ultrasounds, x-rays, blood dI·aws, surgeries, therapies - the list is endless. However, the most challenging aspect of his syndI·ome has been caused by his liver's inability to filter bile efficiently. This causes cholestatic pmritus. Itch. A constant itch that is inside his body. An itch he can never scratch. Nights spent in the hospital full of fear after a surgery is a breeze compared to years upon years of watching your child be tortured by their own bodies. A mother's responsibility is to raise a healthy, safe and happy child. I did not have the ability to achieve that. Night after night I held my son while he screamed in agony and blood dI·ipped from his limbs and face. I rocked him while he cried for help and we sat dI·enched in one another's tears. I watched him be miserable and discontent while other childI·en laughed and learned. I watched his classmates thrive while he was barely smviving Today my son is growing, sleeping, eating and living. He has been using Livmarli since Feb 2021 and the relief from itch has changed all our lives. Chord takes music class, animation lessons, dance training and joined a sledge hockey team. He sleeps more than 2 hours at a time during the night and rarely misses a day of school. Chord is joyfol. He smiles. Our family has a future that isn't shadowed with constant fear and distress. Please do not imprison my son again. Please do not let his body torture him." **-Mom, Tara Jacques**

Royalty, Ontario, Canada - (Referencing a personal posting on Facebook) - *"I hate the "Itch". I hate the way it DRA.INS my family. I want eve1yone to understand the mental, physical, and emotional toll this has on families. It's much more than an insignificant minimized itch. This is torture for everyone, especially our children. It does not stop. There isn't relief It never goes away. One video of 2 minutes.... consider that a glimpse into our entire day."* I literally just reposted that experience before learning about CADTH's recommendation to not reimburse Livmarli. Reading that from 3 years ago, BEFORE sta1ting the dI11g, I felt the pain from my words. It seemed like a lifetime ago! There is a DRASTIC change in Royalty since sta1ting Livmarli. We feel pure happiness about this dI11g. I read these words from 3 years ago, ME, and I felt reliefl I couldI1't breathe back then, but today ! can. Today, my now 9 years old daughter uses her hands to play with toys, write, play guitar/piano. She doesn't sit down at the playground to scratch her limbs, feet, stomach, and ears. She uses her hands to climb up the ladder and slide down the slide!! Royalty is able to go swimming, play spo1ts, go to SCHOOL now, because she isn't trying to lip her clothes off. She isn't COVERED in open sores from NEVERENDING scratching. She's getting full nights of sleeo so she's able to focus and learn and !!:row.

She isn't depending on eve1yone around her to reach that REALLY BAD ITCH. She has ENERGY to nm, play, laugh and enjoy being a CHILD. Her skin doesn't look and feel like rough snake skin and the PAIN is gone." - **Mom, Bonita Irving**

Cloe, Michigan, USA- "I made it a point throughout Cloe's childhood to make itching as easy as possible, allowing her choices and options that would make her as comfortable as possible to scratch freely. However, others in Cloe's life outside of our immediate family did not do that. They did not lmderstand itching and how it affected eve1y aspect of life. She was made to feel unkempt, dirty, and as though she had inept parents eve1y time a teacher, medical professional, or stranger tiied to give lmsolicited advice to her about lotioning her dty scabbed skin or dt·iI1king more water. She was made to feel doubt that I as her mother was taking care of her needs when they would suggest to her that I should take her to the doctor because of the scabbing, bloody wounds, and discomfort. They assumed we didt1't know anything. Our intelligence was low, our common sense was low, our sense of urgency was low.....and her parent was iI1adequate. They made her feel scared to scratch, so she would c1y and suffer silently while being tortured from within. She couldn't focus, would squirm in her seat, and would call me from the school asking me to pick her up. Other people always tlmlk they know better, but in fact they don't see the 27 different ointments and lotions under the bathroom sink. They don't see the 15 different gadgets and tools in her toy box just for scratching or the rolled-up carpets in her closet, each with a different level of rouglmess to fit the severity of itchiness that day. They don't see the specific canvas covered laundt·y baskets and ottomans in our house strategically available so she can stop and scratch on them wherever she is iI1the house whenever she needs to urgently addt·ess a surge of itching. Lastly, because there are alternative dt1 1gs that have been known to"help" with itching, they assume the dtugs help everyone and that we should be satisfied that the 1-10% inconsistent improvement should be enough. Not only do childt·en suffer from the itch, but they are shamed by others' misunderstandings, assumptions, and judgements, as are their parents. Even ifLivmarli only improved itching by 50%, it is so far above any other medication cunently available and wo1th eve1y effo1t of fight we have to beg and plead for its approval. It is nonnalcy, sleep, and energy. It is healiI1 , validation, and a bri 1t future." - **Mom Roberta Smith**

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	X
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	X
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		

a CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information

Name	*Roberta Smith*
Position	*President*
Date	*11-1-2023*
OX	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. **YES**

B. Assistance with Providing Feedback

1. Did you receive help from outside your patient group to complete your feedback?	No	**X**
	Yes	D
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	**X**
	Yes	D
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest

1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	D
	Yes	X

0. New or Updated Conflict of Interest Declaration

3. 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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum Pharmaceuticals	D	D	D	**X**
Add company name	D	D	D	D
Add or remove rows as required	D	D	D	D

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CAOTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: ● Clinician 1 ● Clinician 2 ● *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (OO-MM-YYYY)*
☐	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10.000**	**$10,001 to 50 000**	**In Excess of $50.000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	D

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
	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.

Conflict of Interest Declaration				
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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50 000**	**In Excess of $50 000**
Add company name	☐	☐	☐	☐

Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (OO-MM-YYYY)*
☐	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10 000**	**$10,001 to 50 000**	**In Excess of $50 000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (OO-MM-YYYY)*
☐	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.

Conflict of Interest Declaration

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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information

CADTH project number	SR0780-000
Brand name (generic)	Livmarli (maralixibat)
Indication(s)	Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).
Organization	Children's Liver Disease Foundation
Contact informationa	Name: Michelle Wilkins Email: [redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation. Yes ☐ No

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

As the leading childhood liver disease organisation in the UK, we would like to lend our voice to the recent CADTH reimbursement review in relation to Maralixibat and the Do Not Reimburse recommendation.
We are very disappointed that Alagille's Syndrome patients in Canada will be denied access to a drug that may reduce or remove the severe symptom of cholestatic pruritis due to the decision that the clinical evidence is not sufficient. We are not clinically trained so cannot comment on this, but we believe that there are some issues raised that we can comment on.

P4 bullet point 1 - uncertainty is highlighted. Uncertainty is part and parcel of the world of rare disease and in particular a complex organ such as liver and often even more complex in children than adults. These uncertainties require much increased levels of research to overcome and will take many years due to the little resource this field has in terms of specialists, researchers and patient numbers. Therefore, we would expect small numbers of participants in things like clinical trials and less evidence available.
P4 bullet point 2 - Descriptive evidence is noted as unclear. The very nature of this condition is that it must be described by parent/carers particularly in very young children. An infant cannot explain what this condition feels like and for those children/young people who can describe it this is their 'normal' so they are likely to minimise the severity of the itch and the impact it has as they do not know life without it.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? Yes ☐ No

If not, what aspects are missing from the draft recommendation?

We believe that the impact of pruritus on the lives of patients and their care givers must be given higher significance.
Our organisation has referred patients to CLF in Canada and both organisations discuss the impact of pruritus on patients and their care givers on a regular basis. Without an effective treatment they are dependent on off label alternatives which can be hit and miss in terms of effectiveness. Recently we surveyed 61 Alagille's parent/carers on the impact of pruritus and the responses received gave us

strong evidence of the impact on the patient, on family life and on things like development and education. Please see some direct quotes below:

Impact on child

"My son gets very itchy at times. He scratches his skin until it bleeds sometimes, especially at night. He was mostly NG fed for his first Gyears because he struggles with lack if appetite and struggles to gain weight much".

"When he was a baby ALGS prevented him from gaining weight, he vomited several times a day, the itch stopped him sleeping and made him scratch until he bled. He spent a lot of time crying and needed to be held and distracted. None of the anti-itch meds gave him much relief. Due to his size and lack of muscle tone he had physical developmental delays (sitting up, crawling, walking). He missed the window of opportunity to start eating, so struggled to eat solids and had speech delays."

"He has malnutrition, he has always had issues gaining weight and he now has a peg. The itching it awful. Uncontrollable."

"It is so tough! My son has pulmonary stenosis, intercranial hypertension with papilledema on both his brain and eyes as well as the worst itch. It has a huge impact on his life."

"Very hard. Constant itching, not sleeping. Not eating much so feeding tube."

Impact on the family

"Alagille's has affected the entire family - we had to move countries and continents to get the correct care. Her whole life is curtailed by the disease. It impacts her in every aspect of her life as it affects so many of her organs. Her life is hard with Alagille's. She was transplanted before a year old. It's been hell."

"Pre transplant life was very hard. 23 medications, NG tube and a biliary diversion. Under development, constant itch and debilitated child."

"It's difficult to watch him when he's itching constantly. Our other children get very upset when he has to go to hospital or the fact he has the peg. It has changed our entire family."

"Hugely. Need to distract him from itching. Lack of sleep. Unhappy child generally."

We would therefore fully support reconsideration of this decision, after additional clinical information provided from the drug company alongside any additional patienUcarer impact evidence. A drug within a highly specialised medical area will not be applicable to many but will make a massive difference to the few, which is the nature of rare disease.

"A new drug in the arsenal for treating a debilitating part of the disease. Even for patients considered to have mild disease, the itch feels unbearable. If you'd have told me that a child would talk about endin their life due to itchin , I wouldn't have believed ou, but I've heard it."

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes No	[81 D
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes No	[81 D
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☐ D
Not applicable		

a CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information

Name	*Michelle Wilkins*
Position	*Head of Services*
Date	*27-10-2024*
IZI	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.

B. Assistance with Providing Feedback

1. Did you receive help from outside your patient group to complete your feedback?	No Yes	 ☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No Yes	IZI ☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest

1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section **D** below.	No	IZI ☐

D. New or Updated Conflict of Interest Declaration

3. 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.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Mirum Pharmaceuticals	D	D	IZI	D
Albireo Pharmaceuticals	D	☐	IZI	D

CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

maralixibat (Livmarli)

(Mirum Pharmaceuticals Inc.)

Indication: Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).

April 8, 2024

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0780
Name of the drug and Indication(s)	Maralixibat (Livmarli) for the treatment of cholestatic pruritus in patients with Alagille syndrome.
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance

Version: 1.0
Publication Date: TBC
Report Length: 2 Pages

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. Guidance is required on how to implement renewal criteria for patients who initiate therapy with more severe itch given that they could experience a change of 1 point on the ItchRO (which appears to have been deemed clinically meaningful) and still not achieve a score of 1 or less.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.