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CADTH Reimbursement Review

# Dupilumab (Dupixent)

**Sponsor:** Sanofi-Aventis Canada Inc.

**Therapeutic area:** Atopic dermatitis

Request for Advice  
Stakeholder Input



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Dupilumab (Dupixent)

# Request for Advice



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## Abbreviations

<b>BSA</b>	body surface area
<b>CDEC</b>	CADTH Canadian Drug Expert Committee
<b>CSA</b>	cyclosporine
<b>DLQI</b>	dermatology life quality index
<b>EASI</b>	Eczema Area and Severity Index
<b>IGA</b>	Investigator's Global Assessment
<b>ITC</b>	indirect treatment comparison
<b>NOC</b>	Notice of Compliance
<b>RfA</b>	request for advice
<b>TCS</b>	topical corticosteroid

## Executive Summary

An overview of the request for advice (RfA) for Dupixent (dupilumab) is provided in [Table 1](#).

**Table 1: Overview of the RfA**

Item	Description
Drug (brand)	Dupilumab (Dupixent) solution for subcutaneous injection
Indication	For the treatment of patients aged 12 years and older <sup>a</sup> with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Final CDEC recommendation	Reimburse with clinical criteria and/or conditions ( <a href="#">April 22, 2020</a> )
NOC date	September 25, 2019
Manufacturer	Sanofi-Aventis Canada Inc.
Research question	Should the reimbursement conditions recommended for dupilumab be updated to align with those recommended for upadacitinib and abrocitinib?

CDEC = CADTH Canadian Drug Expert Committee; NOC = Notice of Compliance; RfA = request for advice.

<sup>a</sup>Although dupilumab (Dupixent) is currently approved for patients 6 years of age and older, the request for advice is only for patients aged 12 years and older as per previous final CDEC recommendation.

Source: CDEC Final Recommendation for Dupilumab (Dupixent) for Atopic Dermatitis (2020);<sup>1</sup> Clinical Review Report for Dupilumab (Dupixent) for Atopic Dermatitis (2020).<sup>2</sup>

### Context for RfA

In 2020, the CADTH Canadian Drug Expert Committee (CDEC) recommended that dupilumab be reimbursed for the treatment of atopic dermatitis, only if the conditions for reimbursement were met.<sup>1</sup> One of the conditions for initiation in the recommendation was that patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine (CSA). Furthermore, the prescribing conditions stipulated that the patient must be under the care of a dermatologist.<sup>1</sup>

Subsequently, 3 new drugs for adult patients with moderate-to-severe atopic dermatitis in were reviewed in 2022. CDEC recommended that 2 out of the 3 be reimbursed with clinical criteria and/or conditions (upadacitinib [Rinvoq] and abrocitinib [Cibinqo]), and recommended not to reimburse the third (tralokinumab [Adtralza]).<sup>3-5</sup> While the conditions for reimbursement for upadacitinib and abrocitinib are very similar, they differ from those issued for dupilumab. Based on stakeholder feedback, as the treatments seem to be used similarly in current clinical practice, the public drug plans noted that the discordant reimbursement conditions and criteria may result in implementation challenges.

The public drug programs that participate in the CADTH reimbursement review process are seeking advice on the conditions for reimbursement; specifically, the drug plans asked if reimbursement conditions recommended for dupilumab should be updated to align with those recommended for upadacitinib. Feedback has been received from clinical specialists involved in the diagnosis and management of atopic dermatitis that the criteria included in the dupilumab recommendations are not reflective of current clinical

practice. In particular, the inclusion of a mandatory trial of CSA in the initiation conditions have caused implementation issues for the drug programs.

Dupilumab is currently approved for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. However, the indication originally reviewed by CDEC was for patients aged 12 years and older. The NOC for the expansion in indication from 12 years to 6 years and older was granted in 2021, after the original CDEC review on which this RfA is based.<sup>6</sup> At the time this report was written, dupilumab had not been reviewed by CADTH for this expanded age population of 6 to 11 years in the treatment of atopic dermatitis.

The scope of this RfA report is limited to the question posed by the public drug plans; therefore, only pertinent information necessary to respond to the request is reviewed.

The RfA approach consisted of revisiting pertinent aspects of the CDEC recommendations and reimbursement for dupilumab, upadacitinib, and abrocitinib. Stakeholder input from patient and clinician groups, as well as the manufacturer of Dupixent (dupilumab) was collected. Input from patient and clinician groups was obtained using targeted correspondence with those who have previously participated in reviews for dupilumab, upadacitinib, abrocitinib, and/or tralokinumab for the treatment of atopic dermatitis. In total, 3 patient groups, 3 clinician groups, and Sanofi-Aventis Canada Inc. provided input for this RfA. A clinical expert was also consulted to provide input and insight into the prescribing landscape across Canada.

## Summary of Findings

To reduce implementation challenges that may be faced by public drug plans, the information gathered suggests aligning the following original reimbursement conditions for dupilumab with those for upadacitinib and abrocitinib:

- Initiation criteria:
  - Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
  - Patients who have had an adequate trial of phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.
- Prescribing conditions:
  - The patient must be under the care of a dermatologist.

## Background for This Request for Advice

CDEC has recommended that dupilumab, upadacitinib, and abrocitinib be reimbursed with conditions for the treatment of atopic dermatitis. However, there are differences across the 3 recommendations with respect to these conditions.

The public drug programs that participate in the CADTH reimbursement review process have indicated that the harmonization of reimbursement conditions would help avoid implementation issues that may arise from the CADTH recommendations for dupilumab, upadacitinib, and abrocitinib. In particular, the drug programs have received feedback that the following existing criterion for dupilumab, namely the requirement of CSA, is not supported by a portion of the clinical specialists with expertise in the diagnosis and management of atopic dermatitis: “Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine. Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.” Of note, the drug programs provided similar feedback on the draft recommendation for upadacitinib, and the criterion was revised to provide prescribers with additional flexibility with respect to prior treatment with immunosuppressive agents. The subsequent recommendation for abrocitinib includes reimbursement conditions that are very similar to upadacitinib.

Given the discrepancy between the final recommendations and the feedback received from some clinicians, the drug programs that participate in the CADTH reimbursement review process are requesting that CDEC provide advice regarding the following question:

- Should the reimbursement conditions recommended for dupilumab be updated to align with those recommended for upadacitinib?

### Submission History and CDEC Recommendation for Dupilumab

Dupilumab has been reviewed twice by CADTH for the treatment of atopic dermatitis: as a new drug in 2018, and as a resubmission for a new indication in 2020. The initial review for dupilumab was for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The original CADTH systematic review of dupilumab included 4 double-blind randomized controlled trials (RCTs): the SOLO-1 (N = 671), SOLO-2 (N = 708), LIBERTY AD CAFÉ (N = 325), and LIBERTY AD CHRONOS (N = 740) trials. All trials included patients with moderate-to-severe atopic dermatitis, and patients were randomized to dupilumab every week or every other week, or placebo, for a treatment duration of 16 weeks (SOLO studies and the LIBERTY AD CAFÉ trial) or 52 weeks (the LIBERTY AD CHRONOS trial). In July 2018, CDEC issued a recommendation that dupilumab should not be reimbursed for this indication. Reasons for the CDEC recommendation included the lack of evidence comparing dupilumab to other drugs commonly used for managing atopic dermatitis, the lack of long-term safety data, concerns over generalizability of the data to patients who would be expected to use the drug in clinical practice, and a lack of efficacy and safety data for dupilumab in patients for whom topical prescription therapies are not advisable.<sup>1</sup>

A resubmission was subsequently filed by the sponsor for a new indication, which expanded the initial patient population limited to adults to include adolescents. In April 2020, CDEC issued a recommendation that dupilumab should be reimbursed for the treatment of atopic dermatitis only if the conditions for reimbursement are met.<sup>1</sup> Details of the CDEC recommendation, conditions for reimbursement, reasons for the recommendation, and implementation considerations sections are reported in [Table 2](#).

In 2021, dupilumab received a NOC for an expansion in indication from patients aged 12 years and older to patients aged 6 years and older.<sup>6</sup> Thus, it is currently approved for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. However, this RfA is based on the indication reviewed by CDEC in 2020, for patients aged 12 years and older. The expanded indication with the younger age group had not been reviewed by CADTH at the time the RfA was filed, and thus is out of scope for this review.

## CADTH Approach to the RfA

To address the questions in the RfA, CADTH conducted a detailed comparison of the previous recommendations, reasons for recommendation, and any implementation considerations or guidance to determine the source of discrepancies. A clinical expert was consulted to provide insight into the prescribing landscape across Canada that would directly impact any criteria that could be harmonized. Input was also obtained on the comparison of the place in therapy of dupilumab, upadacitinib, and abrocitinib, considering information previously provided by the clinical expert(s) consulted by the CADTH review team.

Input from patient and clinician groups was also obtained using targeted correspondence with groups who have previously participated in reviews for dupilumab, upadacitinib, abrocitinib, and/or tralokinumab for the treatment of atopic dermatitis. The manufacturer of Dupixent (dupilumab) was also provided with an opportunity to comment on the RfA. CADTH considered the following sources of information to elicit perspectives on the RfA:

- input from 1 clinical expert with experience in treating patients with atopic dermatitis
- input from 3 patient groups: the Eczema Society of Canada, and joint input from the Canadian Skin Patient Alliance and Eczéma Québec (EQ)
- input from 3 clinician groups: the Canadian Dermatology Association, the Dermatologist and Allergist Group Managing Atopic Dermatitis, and Origins Dermatology Centre
- input from Sanofi-Aventis Canada Inc.

## Clinical Findings

### Comparison of CDEC Recommendations

[Table 2](#) summarizes product characteristics as well as CDEC recommendations and reimbursement conditions for dupilumab, upadacitinib, and abrocitinib for the treatment of atopic dermatitis. The difference in numbering and/or formatting is reflective of the changes in processes and reporting structure of CADTH recommendations over time. Key discrepancies in the reimbursement conditions have been bolded under the dupilumab column.

**Table 2: Comparison of Properties and CDEC Recommendations for Dupilumab, Upadacitinib, and Abrocitinib**

Detail	Dupilumab	Upadacitinib	Abrocitinib
<b>Product information</b>			
Brand name	Dupixent	Rinvoq	Cibinqo
Drug class	IL-inhibitor (IL-4 and IL-13)	JAK inhibitor	JAK inhibitor
HC approved indication	Treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.	Treatment of adults and adolescents 12 years of age and older with refractory moderate to severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.	Treatment of patients 12 years and older with refractory moderate to severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable.
Route of administration	Subcutaneous injection	Oral	Oral
Recommended dose	Adults: Initial dose of 600mg, followed by 300 mg every other week. Children and adolescents (6 to 17 years) <sup>a</sup> : Based on weight, given every other week or every 4 weeks.	Adults < 65 years: 15 mg or 30 mg once daily (higher dose for severe disease or inadequate response to 15 mg dose). Adults ≥ 65 years and adolescents (12 to 17 years, ≥ 40 kg): 15 mg once daily.	Adults < 65 years and adolescents (12 to 17 years): 100 or 200 mg once daily. Adults ≥ 65 years: 100 mg once daily.
<b>CDEC final recommendation</b>			
Issued	April 2020	June 2022	August 2022
Recommendation type	Reimburse with conditions	Reimburse with conditions	Reimburse with conditions
Recommendation	CDEC recommends that dupilumab should be reimbursed for the treatment of atopic dermatitis only if the following conditions are met.	CDEC recommends that upadacitinib be reimbursed for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable only if the conditions listed are met.	CDEC recommends that abrocitinib be reimbursed for the treatment of patients aged 12 years and older with refractory moderate to severe AD, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable, only if the conditions listed are met.
<b>Conditions for reimbursement</b>			
Initiation criteria	1. Patients aged 12 years and older with moderate-to-severe AD <b>whose disease is not adequately controlled with topical prescription</b>	1. Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented	1. Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented

Detail	Dupilumab	Upadacitinib	Abrocitinib
	<p>therapies or when those therapies are not advisable.</p> <ol style="list-style-type: none"> <li>Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.</li> <li>Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.</li> <li>The physician must provide the Eczema Area and Severity Index (EASI) score and Physician Global Assessment score at the time of initial request for reimbursement.</li> <li>The maximum duration of initial authorization is six months.</li> </ol>	<p>intolerance), or are ineligible for each of the following therapies:</p> <ol style="list-style-type: none"> <li>maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and</li> <li>maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).</li> </ol> <ol style="list-style-type: none"> <li>The physician must provide the EASI score vIGA-AD score at the time of initial request for reimbursement.</li> </ol>	<p>intolerance), or are ineligible for each of the following therapies:</p> <ol style="list-style-type: none"> <li>Maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and</li> <li>Maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).</li> </ol> <ol style="list-style-type: none"> <li>The physician must provide the EASI score and Investigator (Physician) Global Assessment score at the time of initial request for reimbursement.</li> </ol>
Renewal criteria	<ol style="list-style-type: none"> <li>The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) six months after treatment initiation.</li> <li>The physician must provide proof of maintenance of EASI-75 response from baseline every six months for subsequent authorizations.</li> </ol>	<ol style="list-style-type: none"> <li>The maximum duration of initial authorization is 20 weeks. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI 75) 20 weeks after treatment initiation.</li> <li>For subsequent renewal, the physician must provide proof of maintenance of EASI-75 response from baseline every 6 months for subsequent authorizations.</li> </ol>	<ol style="list-style-type: none"> <li>The maximum duration of initial authorization is 20 weeks. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) 20 weeks after treatment initiation.</li> <li>For subsequent renewal, the physician must provide proof of maintenance of EASI-75 response from baseline every 6 months for subsequent authorizations.</li> </ol>
Prescribing conditions	<ol style="list-style-type: none"> <li>The patient must be under the care of a dermatologist.</li> <li>Dupilumab is not to be</li> </ol>	<ol style="list-style-type: none"> <li>The patient must be under the care of a dermatologist, allergist,</li> </ol>	<ol style="list-style-type: none"> <li>The patient must be under the care of a dermatologist, allergist,</li> </ol>

Detail	Dupilumab	Upadacitinib	Abrocitinib
	used in combination with phototherapy or immunosuppressant drugs, such as methotrexate or cyclosporine.	clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.  2. Upadacitinib should not be used in combination with phototherapy, any immunomodulatory drugs (including biologics) or other JAK inhibitor treatment for moderate to severe AD.	clinical immunologist, or pediatrician who has expertise in the management of moderate-to-severe AD.  2. Abrocitinib should not be used in combination with phototherapy, any immunomodulatory agents (including biologics) or other JAK inhibitor treatment for moderate to severe AD.
Pricing conditions	Reduction in price	Reduction in price	Reduction in price
Feasibility of adoption	N/A	N/A	The feasibility of adoption of abrocitinib must be addressed.
Reason for recommendation			
–	<ol style="list-style-type: none"> <li>Dupilumab demonstrated superiority in improving signs and symptoms of AD, as well as health-related quality of life, when compared with placebo in adolescents (one randomized controlled trial [RCT]), and in adults there were five RCTs) who had moderate-to-severe AD. Patients studied were those with an inadequate response to topical therapies or topical therapies were not advisable (one RCT based on the adolescent population and four RCTs based on the adult population), and where cyclosporine treatment was inadequate, associated with toxicities, or not recommended due to contraindications (1 adult RCT).</li> <li>CDEC discussed patient and clinician input that AD is associated with intense symptoms (namely itching and pain) that can lead to</li> </ol>	<p>Initiation:</p> <p>Conventional approaches to moderate to severe AD refractory to topical therapies have, for a number of years, included older immunomodulatory drugs. Concerns about their long-term safety continue; however, clinical experience with systemic immunomodulators is extensive and the costs are modest compared to novel drugs. CDEC accepted the opinion of the clinical expert and assessments of practice in other jurisdictions and considered that at least 1 conventional immunomodulatory drug be attempted before upadacitinib is used for refractory AD, particularly as information about the long-term safety of the latter is awaited. In addition, the majority of patients enrolled in the trials reviewed by CDEC had a prior exposure to at least 1 systemic therapy for AD, where the percentage of patients with prior exposure to at least 1 systemic treatment for AD in the included trials were: 46.4% in Measure Up 1, 54.5% in Measure Up 2, 66.6% in AD Up, and 51.0% in Heads Up.</p>	<p>Initiation:</p> <p>Conventional approaches to moderate to severe AD refractory to topical therapies have, for a number of years, included older immunomodulatory agents. Concerns about their long-term safety continue; however, clinical experience with systemic immunomodulators is extensive and the costs are modest compared to novel agents. CDEC accepted the opinion of the clinical expert and assessments of practice in other jurisdictions, and considered that at least one conventional immunomodulatory agent be attempted before abrocitinib is used for refractory AD, particularly as information about the long-term safety of the latter is awaited. In addition, in the trials reviewed by CDEC, the percentage of patients with prior exposure to at least one systemic therapy for AD was 48.3% in JADE MONO-1, 41.4% in JADE MONO-2, 43.2% in JADE COMPARE, 47.9% in JADE DARE, 25.6% in JADE TEEN, and 59.5% in JADE REGIMEN. JADE MONO-1, JADE MONO-2,</p>

Detail	Dupilumab	Upadacitinib	Abrocitinib
	<p>sleep disruption, anxiety and depression, social isolation, and impaired quality of life. There are few treatment options after topical therapies and immunosuppressants have failed to improve symptoms. There is limited access to phototherapy across Canada, particularly for patients living in rural areas. CDEC considered that dupilumab would provide a treatment option for patients who have not achieved desired outcomes with adequate trials of topical therapies, phototherapy (where available), and immunosuppressants, or for patients who are ineligible for these therapies or experienced toxicities.</p> <p>3. At the sponsor-submitted price for dupilumab of \$959.94 for each of the 200 mg and 300 mg injections, the incremental cost-effectiveness ratio (ICER) for dupilumab plus standard of care (SOC) vs. SOC alone (topical therapy) was estimated in CADTH's reanalysis to be \$136,025 per additional quality-adjusted life-year (QALY) gained in the Health Canada-indicated population. CADTH reported results of a scenario analysis on the reimbursement request population (patients within the Health Canada indication who were refractory to or ineligible for, systemic immunosuppressant therapies), the estimated</p>	<p>The Measure Up 1, Measure Up 2, AD Up, and Heads Up studies enrolled patients with an EASI score of 16 points or higher, and a vIGA-AD score of 3 or higher.</p> <p>Renewal: CDEC has recommended that the first renewal assessment for upadacitinib occur after 16 to 20 weeks of treatment based on the timing of the primary end point evaluation in the pivotal studies (i.e., EASI-75 at 16 weeks) with 4 weeks of additional flexibility to accommodate scheduling of follow-up evaluations.</p> <p>The clinical expert noted to CDEC that in clinical practice, the response to treatment is assessed 16 to 20 weeks after initiating upadacitinib, then every 6 months thereafter.</p> <p>Prescribing: Accurate diagnosis and follow-up of patients with refractory moderate to severe AD is important to ensure that upadacitinib is prescribed to the most appropriate patients. In addition, there are several treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by dermatologists, allergists, clinical immunologists, or pediatricians who have expertise in the management of moderate to severe AD, and who are familiar with this treatment paradigm.</p> <p>There is no evidence to demonstrate a beneficial effect of upadacitinib when used in combination with phototherapy, any immunomodulatory drugs (including biologics), or other JAK inhibitor treatment for moderate to severe AD.</p> <p>Pricing: The cost-effectiveness of</p>	<p>JADE COMPARE, JADE TEEN, and JADE REGIMEN studies enrolled patients with an EASI score of 16 points or higher, and an Investigator (Physician) Global Assessment score of 3 or higher.</p> <p>Renewal: The clinical expert noted to CDEC that in clinical practice, the response to treatment is assessed 16 to 20 weeks after initiating abrocitinib, then every 6 months thereafter.</p> <p>The primary end point evaluation in the pivotal studies was EASI-75.</p> <p>Prescribing: Accurate diagnosis and follow-up of patient with refractory moderate to severe AD is important to ensure that abrocitinib is prescribed to the most appropriate patients. In addition, there are several treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by dermatologists, allergists, clinical immunologists, or pediatricians who have expertise in the management of moderate to severe AD, and who are familiar with this treatment paradigm.</p> <p>There is no evidence to demonstrate a beneficial effect of abrocitinib when used in combination with phototherapy, any immunomodulatory agents (including biologics), or other JAK inhibitor treatment for moderate to severe AD.</p> <p>Pricing: The ICER for abrocitinib 100 + SoC is \$156,735 per QALY when compared with SOC alone. The ICER for abrocitinib 200 + SoC is \$231,013 per QALY when compared with abrocitinib 100 + SoC.</p>

Detail	Dupilumab	Upadacitinib	Abrocitinib
	<p>ICER was similar (\$133,000 per QALY). In an additional scenario analysis that considered the EASI-75 outcome for treatment response for the Health Canada–indicated population, the ICER was \$120,758 per QALY.</p>	<p>upadacitinib, when administered according to the Health Canada–recommended dosing strategy, is unknown. In an exploratory analysis, no price reduction was necessary for upadacitinib 15 mg to be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY compared to BSC. Exploratory analysis suggested that a price reduction of 35% would be needed for upadacitinib 30 mg to be considered cost-effective compared to upadacitinib 15 mg. Exploratory analysis was performed using the manufacturer’s submitted drug price for upadacitinib and publicly available prices for comparators.</p>	<p>A price reduction of 52% to 56% would be required for abrocitinib to be able to achieve an ICER of \$50,000 per QALY.</p> <p>Feasibility of adoption: At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor’s estimate and CADTH’s estimates.</p>
<b>Implementation considerations or guidance</b>			
<p>–</p>	<ol style="list-style-type: none"> <li>1. Based on the trials, moderate-to-severe AD is defined as an EASI score of 16 points or higher, or an Investigator (Physician) Global Assessment score of three or four.</li> <li>2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the dupilumab RCTs, such as achieving an EASI-75.</li> <li>3. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing dupilumab if otherwise indicated.</li> </ol>	<ol style="list-style-type: none"> <li>1. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing upadacitinib if otherwise indicated.</li> <li>2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the upadacitinib trials, such as achieving EASI-75.</li> <li>3. The clinical expert noted that an “adequate trial” for patients with AD who undergo therapy with phototherapy, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is defined as follows:</li> <li>4. For phototherapy: the typical duration would be considered 12 weeks (3 times per week).</li> </ol>	<ol style="list-style-type: none"> <li>1. Phototherapy may not be available in all jurisdictions. Geographic inability to access phototherapy should not preclude patients from accessing abrocitinib if otherwise indicated.</li> <li>2. Adequate control and refractory disease are optimally defined using similar criteria to those used in the abrocitinib trials, such as achieving an EASI-75.</li> <li>3. The clinical expert noted that an “adequate trial” for patients with AD who undergo therapy with phototherapy, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine is defined as follows:               <ol style="list-style-type: none"> <li>3.1. For phototherapy: the typical duration would be considered 12 weeks (3 times per week).</li> </ol> </li> </ol>

Detail	Dupilumab	Upadacitinib	Abrocitinib
		4.1. For methotrexate: an adequate trial would be 10 mg to 20 mg per week for 12 weeks. 4.2. For cyclosporine: an adequate trial would be 2.5 mg/kg to 5 mg/kg per day for 12 weeks. 4.3. For mycophenolate mofetil: an adequate trial would be 1 g twice daily for 12 weeks. 4.4. For azathioprine: an adequate trial would be 1.5 to 2.5 mg/kg/day for 12 weeks.	3.2. For methotrexate: an adequate trial would be 10 to 20 mg per week for 12 weeks. 3.3. For cyclosporine: an adequate trial would be 2.5 mg/kg/day to 5 mg/kg/day for 12 weeks. 3.4. For mycophenolate mofetil: an adequate trial would be 1 g twice daily for 12 weeks. 3.5. For azathioprine: an adequate trial would be 1.5 mg/kg/day to 2.5 mg/kg/day for 12 weeks.

AD = atopic dermatitis; BSC = best supportive care; CDEC = CADTH Canadian Drug Expert Committee; EASI = Eczema Area and Severity Index; HC = Health Canada; IL = interleukin; JAK = Janus Kinase; QALY = quality-adjusted life-year; RCT = randomized controlled trial; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

<sup>a</sup>Although dupilumab (Dupixent) is currently approved for patients aged 6 years and older, the request for advice is only for patients aged 12 years and older, as per the previous final CDEC recommendation.

Source: Dupixent Product Monograph;<sup>7</sup> Rinvoq Product Monograph;<sup>8</sup> Abrocitinib Product Monograph;<sup>9</sup> CDEC Final Recommendation for Dupilumab (Dupixent) for Atopic Dermatitis (2020);<sup>1</sup> CDEC Final Recommendation for Upadacitinib (Rinvoq) for Atopic Dermatitis (2022);<sup>3</sup> CDEC Final Recommendation for Abrocitinib (Cibinqo) for Atopic Dermatitis (2022).<sup>4</sup>

## Relevant Details of Included Studies in the CADTH Reimbursement Review for Dupilumab

### Studies Included in the Clinical Review of Dupilumab

The 2020 review of dupilumab included 6 double-blind RCTs, 4 from the initial review conducted in 2018 (the SOLO-1 and SOLO-2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials) as well as 2 new studies: 1 in adolescents (Study 1526) and 1 in adults (the SOLO CONTINUE trial) who had moderate to severe AD.<sup>1</sup>

[Table 3](#) and [Table 4](#) outline key details of each trial included in the 2020 dupilumab review.

### Adolescents (Aged 12 to Younger Than 18 Years)

One pivotal sponsor-funded, phase III, double-blind RCT, Study 1526, which featured a population of 251 adolescents with moderate-to-severe AD, was included in the review. Study 1526 was a 16-week comparison of 2 different dose regimens of dupilumab, administered every 4 weeks or every 2 weeks to matching placebo, with the strength of dose (200 mg or 300 mg) determined by weight (< 60 kg or ≥ 60 kg). The every-2-weeks regimen was the focus of the review, as it is the 1 approved by Health Canada. Patients were those who had demonstrated a recent history of inadequate response to topical therapies, or for whom topicals were not advised (due to intolerance, side effects, or safety risk). The primary outcome varied depending on geographic region; for patients in the US and US reference-market countries, the primary outcome was patients with an Investigator Global Assessment (IGA) score of 0 or 1 at week 16, while EU and EU

reference-market countries added the coprimary outcome of patients achieving Eczema Area and Severity Index (EASI)-75 at week 16. Key secondary outcomes included percent change from baseline to week 16 in EASI, weekly average of daily peak pruritus numeric rating scale (NRS), and patients with an improvement of greater than or equal to 3 or greater than or equal to 4 in weekly average of daily peak pruritus NRS. Randomization was conducted using an interactive voice response system and was stratified by weight (< 60 kg or ≥ 60 kg) and disease severity at baseline (moderate [IGA score of 3] or severe [IGA score of 4]). Aside from the data management committee, all individuals involved in the study remained blinded until the prespecified unblinding. The study began with a screening period of up to 5 weeks during which patients were assessed for study eligibility, and systemic and topical treatments for AD were washed out, according to eligibility requirements.<sup>2</sup>

### **Adults**

The SOLO CONTINUE trial was a phase III, double-blind, placebo-controlled RCT that sought to determine which dosage regimens of dupilumab would be able to maintain the treatment response achieved in the initial 16-week studies, SOLO-1 and SOLO-2. Patients who had achieved an IGA score of 0 or 1 or EASI-75 in these initial studies were randomized to either the same regimen they received in the SOLO-1 or SOLO-2 trials (dupilumab every 2 weeks or weekly), or dupilumab every 4 weeks, dupilumab every 8 weeks, or matched placebo. Patients who received placebo in the initial studies were eligible to enrol in the SOLO CONTINUE trial to maintain blinding, but were not randomized. Instead, they simply received placebo for the duration of the study and were not included in efficacy analyses. An interactive voice response system/interactive web response system was used, and randomization was stratified by the original dupilumab regimen used in the parent study, region (North America, Europe, Asia, Japan), and baseline IGA (0 versus 1 versus > 1). Patients began treatment following randomization on day 1 (week 16 of the initial study) and underwent a 36-week treatment period and a 12-week follow-up period.<sup>2</sup>

The evidence presented for adults in the 2018 review was acquired from 4 sponsor-funded phase III RCTs (the SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials). The SOLO 1 and SOLO 2 trials were 16-week, randomized, double-blind, placebo-controlled, parallel-group trials. Patients in the SOLO trials were recruited globally and randomized for treatment with dupilumab 600 mg on day 1, followed by 300 mg weekly subcutaneous injections for 16 weeks, dupilumab 600 mg on day 1, followed by 300 mg subcutaneous injections every other week for 16 weeks, or weekly matched subcutaneous injections of placebo. The Health Canada–recommended dose of 300 mg dupilumab once every other week was the focus of the review. SOLO 1 and SOLO 2 randomized 671 and 708 patients, respectively. Patients in the SOLO trials were included if topical atopic dermatitis treatment was inadvisable or provided inadequate treatment. Following completion of the 16-week trial, patients were either followed up for an additional 12 weeks or transitioned to an open-label or maintenance study. The LIBERTY AD CHRONOS trial was similar to the SOLO trials but was 52 weeks in duration, and either followed up for an additional 12 weeks or transitioned to an open-label extension study. Patients were included if topical treatment provided inadequate response and patients who experienced important side effects to topical medications (e.g., intolerance and hypersensitivity) were excluded. In the LIBERTY AD CHRONOS trial, 740 patients recruited from North America, Europe, and Asia were randomized, with data from 623 patients available at the time of review.

The inclusion and exclusion criteria in the LIBERTY AD CHRONOS trial were also reflected in criteria for the LIBERTY AD CAFÉ trial, with the additional inclusion criteria of a history of prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or patients had to have a history of being CSA-naive and not eligible for CSA due to medical contraindications or other reasons. The LIBERTY AD CAFÉ trial was a 16-week trial similar to the LIBERTY AD CHRONOS trial; in the LIBERTY AD CAFÉ trial, 325 patients were randomized to 1 of 3 groups with concomitant use of a TCS.<sup>2</sup>

All patients in the LIBERTY AD CHRONOS and LIBERTY AD CAFÉ trials were required to use a medium-potency topical corticosteroid (TCS) on active lesions. In the SOLO trials, use of any TCS was classified as rescue. Across all studies, the proportion of patients achieving EASI-75 at week 16 was the primary efficacy end point. The proportion of patients with an IGA score of 0 or 1 (on a 5-point scale) and a reduction from baseline of 2 or more points at week 16 was an additional primary end point for the SOLO trials and LIBERTY AD CHRONOS, and a secondary end point for LIBERTY AD CAFÉ. Secondary end points assessing atopic dermatitis severity (i.e., Scoring Atopic Dermatitis [SCORAD]), atopic dermatitis symptoms (pruritus NRS, POEM), and health-related quality of life (dermatology life quality index [DLQI] and EuroQol 5-Dimensions [EQ-5D]) were consistent across all trials.<sup>2</sup>

**Table 3: Study Included in the Clinical Review for Dupilumab (Adolescent Population)**

Detail	Study 1526
Study design	DB RCT
Randomized (N)	251
Inclusion criteria	<ul style="list-style-type: none"> <li>• Male or female, ≥ 12 to &lt; 18 years of age</li> <li>• Diagnosis of AD according to the American Academy of Dermatology consensus criteria (Eichenfield [2014]) at screening visit</li> <li>• Chronic AD diagnosed at least 1 year before the screening visit</li> <li>• IGA ≥ 3 at the screening and baseline visits</li> <li>• EASI ≥ 16 at the screening and baseline visits</li> <li>• Baseline pruritus NRS average score for maximum itch intensity ≥ 4</li> <li>• ≥ 10% BSA of AD involvement at the screening and baseline visits</li> <li>• Documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s), or being a person for whom topical treatments were medically inadvisable (e.g., intolerance because of important side effects or safety risks)</li> <li>• Applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (refer to exclusion criteria regarding restrictions on the kind of emollients permitted during the study)</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Treated with a TCS or TCI within 2 weeks before the baseline visit (patients were permitted to rescreen)</li> <li>• Used any of the following treatments within 4 weeks before the baseline visit, or had any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 4 weeks of study treatment:               <ul style="list-style-type: none"> <li>◦ immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, ciclosporin, mycophenolate mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate)</li> <li>◦ phototherapy for AD</li> </ul> </li> </ul>

Detail	Study 1526
	<ul style="list-style-type: none"> <li>Treated with biologics, as follows:               <ul style="list-style-type: none"> <li>any cell-depleting agents, including but not limited to rituximab within 6 months before the baseline visit, or until lymphocyte and CD19+ lymphocyte counts returned to normal, whichever was longer</li> <li>other biologics within 5 half-lives (if known) or 16 weeks before the baseline visit, whichever was longer</li> </ul> </li> <li>Treated with crisaborole within 2 weeks before the baseline visit</li> <li>Body weight &lt; 30 kg at baseline</li> <li>Initiated treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients were permitted to continue using stable doses of such moisturizers if initiated before the screening visit)</li> </ul>
<b>Intervention</b>	Dupilumab SC q.2.w. treatment: <ul style="list-style-type: none"> <li>If &lt; 60 kg: 400 mg loading dose on day 1, then 200 mg q.2.w. from week 2 to week 14</li> <li>If ≥ 60 kg: 600 mg loading dose on day 1, then 300 mg q.2.w. from week 2 to week 14</li> </ul> Dupilumab SC q.4.w treatment: 600 mg loading dose on day 1, then 300 mg q.4.w. from week 4 to week 12; to maintain the blind, there was an SC injection of placebo in between dupilumab doses during the dosing period between week 2 and week 14, so the injection frequency matched the other 2 groups
<b>Comparator(s)</b>	Placebo q.2.w.
<b>Phase</b>	
Double-blind	16 weeks
Follow-up	12 weeks
<b>Primary end point</b>	Patients with IGA 0 or 1 (on a 5-point scale) at week 16. The coprimary end points in the study for EU and EU reference-market countries were: <ul style="list-style-type: none"> <li>Proportion of patients with EASI-75 (≥ 75% improvement from baseline) at week 16</li> <li>Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16</li> </ul> Because Health Canada used coprimary outcomes in their analysis, this is the approach that was taken in the review.

AD = atopic dermatitis; BSA = body surface area; DB = double-blind; EASI = Eczema Area and Severity Index; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EU = European Union; IGA = Investigator's Global Assessment; NRS = numerical rating scale; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; RCT = randomized controlled trial; SC = subcutaneous; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Source: Adapted from Clinical Review Report for Dupilumab (Dupixent) for Atopic Dermatitis (2020).<sup>2</sup>

**Table 4: Studies Included in the Clinical Review for Dupilumab (Adult Population)**

Detail	SOLO 1	SOLO 2	SOLO CONTINUE	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
<b>Study design</b>	DB RCT	DB RCT	DB RCT	DB RCT	DB RCT
<b>Randomized (N)</b>	671	708	Patients enrolled in SOLO 1 and SOLO 2	740	325

Detail	SOLO 1	SOLO 2	SOLO CONTINUE	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
<b>Inclusion criteria</b>	<p>Male and female patients <math>\geq 18</math> years of age, with moderate-to-severe AD with an IGA score <math>\geq 3</math>, EASI score <math>\geq 16</math>, <math>\geq 10\%</math> BSA with AD, for whom topical treatment was inadvisable or provided inadequate treatment</p> <p>Patients had to have chronic AD for a minimum of 3 years</p>	<p>Male and female patients <math>\geq 18</math> years of age, with moderate-to-severe AD with an IGA score <math>\geq 3</math>, EASI score <math>\geq 16</math>, <math>\geq 10\%</math> BSA with AD, for whom topical treatment was inadvisable or provided inadequate treatment</p> <p>Patients had to have chronic AD for a minimum of 3 years</p>	<p>Completed the treatment phase in 1 of the two 16-week initial-treatment studies (SOLO 1 or SOLO 2); achieved at least 1 of the following 2 treatment success criteria:</p> <p>IGA = 0 or 1 (clear or almost clear) at week 16 or EASI-75 from baseline to week 16</p>	<p>Male and female patients <math>\geq 18</math> years of age, with moderate-to-severe AD with an IGA score <math>\geq 3</math>, EASI score <math>\geq 16</math>, <math>\geq 10\%</math> BSA with AD, for whom topical treatment provided inadequate response</p> <p>Patients had to have chronic AD for a minimum of 3 years</p>	<p>Male and female patients <math>\geq 18</math> years of age, with chronic AD with an IGA score <math>\geq 3</math>, EASI score <math>\geq 20</math>, <math>\geq 10\%</math> BSA with AD, for whom treatment with a potent TCS was indicated, but had inadequate response to TCS</p> <p>History of:</p> <ul style="list-style-type: none"> <li>• Prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or</li> <li>• CSA-naïve and not eligible for CSA due to medical contraindications, use of prohibited concomitant medications, increased susceptibility to CSA-induced renal damage and/or liver damage, increased risk of serious infection, or hypersensitivity to CSA-active substances or excipients</li> </ul>
<b>Exclusion criteria</b>	<p>Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive and/or immunomodulating drugs or phototherapy within</p>	<p>Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive and/or immunomodulating drugs or phototherapy within</p>	<p>Receipt of rescue medication for AD in the initial-treatment study (i.e., the parent studies SOLO 1 or SOLO 2)</p>	<p>Participation in prior dupilumab clinical study, important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic</p>	<p>Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, hypersensitivity/intolerance to a TCS, treatment with systemic CSA, systemic corticosteroids,</p>

Detail	SOLO 1	SOLO 2	SOLO CONTINUE	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
	4 weeks of baseline visit, treatment with a TCS or TCI within 1 week before baseline visit, treatment with biologics within 6 months of the baseline visit	4 weeks of baseline visit, treatment with a TCS or TCI within 1 week before baseline visit, treatment with biologics within 6 months of the baseline visit		effects), as assessed by the investigator or the patient's treating physician, $\geq 30\%$ of the total lesional surface located on areas of thin skin that could not be safely treated with a medium or higher-potency TCS; treatment with a TCS or a TCI within 1 week before the baseline visit	or phototherapy within 4 weeks of screening, treatment with a TCI within 1 week before screening visit
<b>Intervention</b>	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. for 16 weeks	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. for 16 weeks	Patients who received 300 mg q.w. in the initial studies: randomized 2:1:1:1 into 1 of 4 treatment regimens, consisting of dupilumab 300 mg given either q.w., q.4.w., or q.8.w., or placebo Patients who received 300 mg q.2.w. in the initial studies: randomized 2:1:1:1 into 1 of 4 treatment regimens consisting of dupilumab 300 mg q.2.w., q.4.w., or q.8.w., or placebo	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. plus TCS for 16 weeks	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks
<b>Comparator(s)</b>	Placebo	Placebo	Placebo weekly	Placebo plus TCS	Placebo plus TCS
<b>Double-blind</b>	16 weeks	16 weeks	36 weeks	52 weeks	16 weeks
<b>Follow-up</b>	Week 16, 28	Week 16, 28	12 weeks	Week 16, 52, 64	Week 16, 28
<b>Primary end points</b>	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16 Proportion of patients with $\geq 75\%$	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16 Proportion of patients with $\geq 75\%$	Difference between baseline (week 0) and week 36 in percent change in EASI from the baseline in the parent study (SOLO 1 or SOLO 2) for all	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16 Proportion of patients with $\geq 75\%$	Proportion of patients with $\geq 75\%$ improvement on the EASI at week 16

Detail	SOLO 1	SOLO 2	SOLO CONTINUE	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
	improvement on the EASI at week 16	improvement on the EASI at week 16	randomized patients Patients with EASI-75 at week 36 in randomized patients with EASI-75 at baseline (of the current study)	improvement on the EASI at week 16	

AD = atopic dermatitis; BSA = body surface area; CSA = cyclosporine-A; DB = double-blind; EASI = Eczema Area and Severity Index; EASI-75 = Eczema Area and Severity Index score improvement from baseline  $\geq$  75%; IGA = Investigator's Global Assessment; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.w. = every week; RCT = randomized controlled trial; SC = subcutaneous; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Source: Adapted from Clinical Review Report for Dupilumab (Dupixent) for Atopic Dermatitis (2020).<sup>2</sup>

### ***Outcome Measures of Interest***

The following provides brief descriptions of the outcomes which were included in the clinical review of dupilumab as well as the reimbursement recommendation and conditions for dupilumab.

IGA is a 5-point scale that provides a global clinical assessment of atopic dermatitis severity (ranging from 0 to 4). A score of 0 indicates clear, and 4 indicates severe atopic dermatitis. A decrease in score relates to an improvement in signs and symptoms. No information was found on what would constitute a minimum importance difference (MID) in patients with atopic dermatitis.<sup>2</sup>

EASI is a scale used in clinical trials to assess the severity and extent of atopic dermatitis. With EASI, 4 disease characteristics of atopic dermatitis (erythema, infiltration/papulation, excoriations, and lichenification) are assessed for severity by the investigator on a scale of 0 (absent) to 3 (severe), and the scores are added up for each of the 4 body regions (head, arms, trunk, and legs). The assigned percentages of body surface area (BSA) for each section of the body are 10% for head, 20% for arms, 30% for trunk, and 40% for legs respectively. Each subtotal score is multiplied by the BSA represented by that region. In addition, the affected area of atopic dermatitis assessed as a percentage by each body region is converted to a score of 0 to 6, where the area is expressed as 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores are multiplied by the area affected. Therefore, the total EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD. It is suggested that the severity of AD based on EASI be categorized as follows: 0 represents clear; 0.1 to 1.0 represents almost clear; 1.1 to 7.0 represents mild; 7.1 to 21.0 represents moderate; 21.1 to 50.0 represents severe; and 50.1 to 72.0 represents very severe. EASI-75 indicates a 75% or greater improvement from baseline. The overall MID is 6.6, based on results from 1 study.<sup>2</sup>

### **Relevant Baseline Characteristics of Patients Enrolled in the Studies Included in the Clinical Review of Dupilumab**

Only details relevant to understanding the formation of the reimbursement conditions for dupilumab are discussed in this section. For further detail, consult documents from the 2020 review (e.g., the [Clinical Review Report](#)) on the CADTH website.

In Study 1526, 7% of patients treated with dupilumab versus 11% of patients treated with placebo discontinued treatment, while across the other studies in adults, between 0% and 9% discontinued in the dupilumab groups and between 5% and 20% discontinued in the placebo groups. Limitations of the included trials included the lack of an active comparator, as all trials were placebo-controlled, of relatively short duration, and excluded patients who used topical calcineurin inhibitors (TCIs) or TCSs within 1 to 2 weeks before the baseline or screening visit.<sup>1</sup>

Of the patients enrolled in Study 1526 involving adolescents (12 to < 18 years old), more than half were male, about 60% were white, and the average age was 14.5 years. Patients had atopic dermatitis for approximately 12 years, on average; 47% had an IGA score of 3 (moderate atopic dermatitis) and 53% had an IGA score of 4 (severe atopic dermatitis). Approximately 40% had received prior corticosteroids or immunosuppressants for their atopic dermatitis.<sup>2</sup>

For studies involving adult patients, in the SOLO CONTINUE trial, the average age of patients was approximately 38 years, 53% were male, and 71% were white. The majority of patients (77%) had an IGA score of 0 or 1 at baseline, as these were all patients who were responders in the SOLO 1 and SOLO 2 trials. The SOLO trials and the LIBERTY AD CHRONOS trial recruited patients globally, with 34.0% to 49.2% of patients living in North and South America. The LIBERTY AD CAFÉ trial recruited patients from Europe, with approximately 62% originating from Western Europe and more than 96% identifying as white. Across trials, the baseline disease characteristics were balanced between groups for each study. The majority of patients, ranging from 52.2% to 68.2%, were diagnosed with atopic dermatitis before the age of 5. Despite varying inclusion criteria, baseline severity of disease was similar between studies for various measures including the EASI, IGA, weekly average of peak daily pruritus NRS, and SCORAD.<sup>2</sup>

**Table 5: Summary of Relevant Baseline Characteristics: Studies Included in the Clinical Review for Dupilumab (Adolescent Population)**

Characteristic	Study 1526	
	Dupilumab q.2.w. N = 82	Placebo N = 85
Mean (SD) age, years	14.5 (1.7)	14.5 (1.8)
Mean duration of atopic dermatitis, years (SD)	12.5 (2.97)	12.3 (3.44)
EASI score mean (SD)	35.3 (13.84)	35.5 (13.97)
IGA score mean (SD)	3.5 (0.50)	3.5 (0.50)
Number n (%) of patients with IGA score		
IGA = 3	39 (48)	39 (46)
IGA = 4	43 (52)	46 (54)
Peak weekly averaged pruritus NRS mean (SD)	7.5 (1.52)	7.7 (1.62)
Patients receiving prior systemic corticosteroids and/or systemic nonsteroidal immunosuppressants, n (%)	35 (43)	33 (39)

Characteristic	Study 1526	
	Dupilumab q.2.w. N = 82	Placebo N = 85
Patients receiving prior systemic corticosteroids, n (%)	21 (26)	21 (25)
Patients receiving prior systemic nonsteroidal Immunosuppressants, n (%)	20 (24)	17 (20)
Azathioprine	0	1 (1)
Cyclosporine	14 (17)	12 (14)
Methotrexate	10 (12)	6 (7)
Mycophenolate	2 (2)	0

EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scale; q.2.w. = every 2 weeks; SD = standard deviation.

Source: Adapted from Clinical Review Report for Dupilumab (Dupixent) for Atopic Dermatitis (2020).<sup>2</sup>

**Table 6: Summary of Relevant Baseline Characteristics: Studies Included in the Clinical Review for Dupilumab (Adult Population)**

Detail	SOLO 1		SOLO 2		SOLO CONTINUE		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dup 300 mg q.2.w. N = 224	Placebo N = 224	Dup 300 mg q.2.w. N = 233	Placebo N = 236	Dup q.2.w./ q.w. N = 167	Placebo N = 83	Dup 300 mg q.2.w + TCS N = 106	Placebo + TCS N = 315	Dup 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Age, years mean (SD)	39.8 (14.7)	39.5 (13.9)	36.9 (14.0)	37.4 (14.1)	38.5 (13.94)	38.1 (13.64)	39.6 (14.0)	36.6 (13.0)	37.5 (12.9)	38.9 (13.4)
<b>Inadequate response to TCS treatment, n (%)</b>										
No	5 (2.2)	4 (1.8)	4 (1.7)	6 (2.5)	NA	NA	NA	NA	NA	NA
Significant skin atrophy	0	2 (0.9)	2 (0.9)	4 (1.7)	NA	NA	NA	NA	NA	NA
Hypersensitivity reactions	1 (0.4)	2 (0.9)	2 (0.9)	2 (0.8)	NA	NA	NA	NA	NA	NA
Systemic effects	2 (0.9)	1 (0.4)	1 (0.4)	0	NA	NA	NA	NA	NA	NA
Other	2 (0.9)	0	1 (0.4)	1 (0.4)	NA	NA	NA	NA	NA	NA
Duration of AD, years, mean (SD)	28.5 (16.1)	29.5 (14.5)	27.2 (14.2)	28.2 (14.4)	NA	NA	30.1 (15.5)	27.5 (14.3)	29.6 (15.6)	29.2 (14.7)
EASI score, mean (SD)	33.0 (13.6)	34.5 (14.5)	31.8 (13.1)	33.6 (14.3)	2.6 (2.9)	2.5 (2.3)	33.6 (13.3)	32.6 (12.9)	33.5 (10.5)	34.4 (10.1)
IGA score, mean (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	NR	NR	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)

Detail	SOLO 1		SOLO 2		SOLO CONTINUE		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dup 300 mg q.2.w. N = 224	Placebo N = 224	Dup 300 mg q.2.w. N = 233	Placebo N = 236	Dup q.2.w./q.w. N = 167	Placebo N = 83	Dup 300 mg q.2.w + TCS N = 106	Placebo + TCS N = 315	Dup 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Patients whose IGA = 3, n (%)	234 (50.9) pooled SOLO 1/2	234 (51.2) pooled SOLO 1/2	234 (50.9) pooled SOLO 1/2	234 (51.2) pooled SOLO 1/2	3 (2)	1 (1)	NR	NR	NR	NR
Patients whose IGA = 4, n (%)	225 (48.9) Pooled SOLO 1/2	223 (48.8) SOLO 1/2	225 (48.9) Pooled SOLO 1/2	223 (48.8) SOLO 1/2	0	0	NR	NR	NR	NR
<b>Weekly average of peak daily pruritus NRS, mean (SD)</b>	7.2 (1.9) <sup>a</sup>	7.4 (1.8) <sup>a</sup>	7.6 (1.60) <sup>a</sup>	7.5 (1.8) <sup>a</sup>	2.8 (1.92)	2.8 (2.11)	7.4 (1.7) <sup>a</sup>	7.3 (1.8) <sup>a</sup>	6.4 (2.2) <sup>a</sup>	6.4 (2.2) <sup>a</sup>

AD = atopic dermatitis; Dup = dupilumab; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NA = not applicable; NR = not reported; NRS = numerical rating scale; q.2.w. = every 2 weeks; q.w. = weekly; SD = standard deviation; TCS = topical corticosteroid.

<sup>a</sup>Weekly average obtained in the 7-day period before the baseline visit.

Source: Adapted from Clinical Review Report for Dupilumab (Dupixent) for Atopic Dermatitis (2020).<sup>2</sup>

Additionally, for the purpose of this RfA, the original studies included in the 2020 clinical assessment of dupilumab were reviewed to provide further context on the number of patients who received at least 1 prior systemic immunosuppressants. A description of data for the included studies regarding the percentages of patients who received at least 1 prior systemic immunosuppressant, including azathioprine, CSA, methotrexate, and mycophenolate, are as follows:

In Study 1526, the percentages of patients who received at least 1 prior systemic immunosuppressants were 20.8% (52 of 250) in total participants, 20% (17 of 85) in patients who had received placebo, 24.4% (20 of 82) in patients treated with dupilumab 200 mg or 300 mg every 2 weeks, 18.1% (15 of 83) in patients receiving dupilumab 300 mg every 4 weeks., and 21.2% (35 of 165) in all patients who had been treated with dupilumab.<sup>10</sup>

In the SOLO 1 study, the percentages were █████ in total participants, 23.9% (53 of 222) in patients who had received placebo weekly, 26.6% (61 of 229) in patients treated with dupilumab 300 mg every 2 weeks, 28.4% (62 of 218) in patients receiving dupilumab 300 mg weekly, and █████ in all patients who had been treated with dupilumab.<sup>10</sup>

In the SOLO 2 study, the percentages were █████ in total participants, 29.9% (70 of 234) in patients who had received placebo weekly, 32.2% (76 of 236) in patients treated with dupilumab 300 mg every 2 weeks, 31.2%

(74 of 237) in patients receiving dupilumab 300 mg weekly, and [REDACTED] in all patients who had been treated with dupilumab.<sup>10</sup>

In the LIBERTY AD CHRONOS study, the percentages were 33.6% ([REDACTED]) in total participants, [REDACTED] in patients who had received placebo weekly plus TCSs, [REDACTED] in patients treated with dupilumab 300 mg every 2 weeks plus TCS, [REDACTED] in patients receiving dupilumab 300 mg weekly plus TCS, and [REDACTED] in all patients who had been treated with dupilumab plus TCS.<sup>10</sup>

In the LIBERTY AD CAFÉ study, the percentages were [REDACTED] in total participants, 77.8% (84 of 108) in patients who had received placebo weekly plus TCS, 78.5% (84 of 107) in patients treated with dupilumab 300 mg every 2 weeks plus TCS, 76.4% (84 of 110) in patients receiving dupilumab 300 mg weekly plus TCS, and [REDACTED] in all patients who had been treated with dupilumab plus TCS.<sup>10</sup>

## Conclusions From the Clinical Review of Dupilumab

The primary clinical conclusions from the 2020 CADTH reimbursement review of dupilumab were as follows:

Six double-blind RCTs in patients with moderate-to-severe atopic dermatitis – 4 in adults from the original review of dupilumab (SOLO 1 and 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ), 1 in adolescents (Study 1526), and 1 longer-term extension in adults (SOLO CONTINUE) – were included in this review. In both adults and adolescents, dupilumab improved various measures of disease severity (IGA, EASI), symptoms (pruritus), and health-related quality of life (DLQI or Children’s DLQI) compared with placebo after 16 weeks (and 52 weeks with LIBERTY AD CHRONOS) of treatment. Where the minimum clinically important differences were known, these differences were clinically significant. Results from SOLO CONTINUE suggest durability of the effects after an initial 16-week treatment response; however, longer-term studies are needed. No direct comparisons of dupilumab to other systemic therapies for atopic dermatitis were found, and published indirect treatment comparisons ITCs were inconclusive due to poor methodological quality and limitations with the base data. There was no clear evidence of important harms occurring at greater risk with dupilumab than placebo, and longer-term safety extensions in both adolescents and adults revealed no new safety signals, with a mean follow-up of an additional 26 and 38 weeks, respectively.<sup>2</sup>

## Stakeholder Perspectives

### Patient Group Input

Input was received from 3 patient groups. A joint input was submitted by 2 patient groups, the Canadian Skin Patient Alliance and Eczéma Québec (EQ), and another input was submitted from the Eczema Society of Canada.

Overall, all the patient groups agreed that some reimbursement conditions recommended for dupilumab should be updated to align with those recommended for upadacitinib. Highlights of points made by the patient groups include the following:

- The Canadian Skin Patient Alliance and EQ proposed that the initiation criteria for dupilumab should be updated to echo the initiation criteria for upadacitinib.
- The Eczema Society of Canada raised concerns about requiring patients to be unresponsive to multiple off-label medications before accessing the approved medications, noting that this could pose barriers and appears unreasonable and inequitable.
- All patient groups agreed that patients should be under the care of specialists who have expertise in the management of moderate-to-severe atopic dermatitis and advanced therapies. The Canadian Skin Patient Alliance and EQ specifically noted that the prescribing conditions recommended for dupilumab should be changed to align with the condition recommended for upadacitinib: “The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.”

Conversely, the Canadian Skin Patient Alliance and EQ did not agree with updating the recommended renewal criteria that differ for dupilumab. Specifically, the Canadian Skin Patient Alliance and EQ recommended keeping the current duration of initial authorization to 6 months, with the rationale that this duration reflected the unique considerations for dupilumab. They also proposed involvement of special sites to be included as part of the initiation criteria as an alternative to meeting the criteria for overall severity. Details can be found in the full Stakeholder Input section at the end of this report.

## Clinical Expert Input

The information in this section is a summary of input provided by the clinical expert consulted by CADTH.

### Description of the Current Treatment Paradigm for the Disease

Presently, patients achieving suboptimal disease control with appropriate disease-specific skin care measures (irritant avoidance, emollients, bleach baths, and so forth), TCSs, calcineurin inhibitors, crisaborole, or phototherapy (if available) are offered treatment with off-label systemic immunosuppressive agents.

In Canada, the most commonly prescribed systemic immunosuppressive drug for atopic dermatitis is methotrexate, followed by CSA, mycophenolate mofetil, and azathioprine. Because of their potential toxicities, these drugs are generally prescribed as intermittent courses in atopic dermatitis. There are patients for whom some or all of these drugs are contraindicated and/or for whom toxicities limit their use. There are also patients who do not respond to any of these drugs. Following trials of immunosuppressive agents, dupilumab, upadacitinib, and abrocitinib are anticipated to be offered as second-line systemic therapy.

### Place in Therapy

Dupilumab, upadacitinib, and abrocitinib are potentially useful additions to the currently available therapeutic options for atopic dermatitis, with special consideration for patients who have contraindications to, experience adverse effects from, or are unresponsive to off-label systemic immunosuppressive agents. They could also be useful in the subset of patients who respond to off-label immunosuppressive agents but require prolonged continuous immunosuppressive therapy for control of atopic dermatitis.

Ideally, it would be appropriate to recommend trials of 2 systemic immunosuppressives (e.g., methotrexate and CSA) before initiating treatment with dupilumab, upadacitinib, or abrocitinib. These older agents are efficacious, and dermatologists are well versed in appropriate dosing, duration of therapy, and monitoring of patients for potential toxicities. In addition, many patients can be managed with intermittent courses of immunosuppressives. As the patient population who would be eligible for treatment with the second-line systemic therapies dupilumab, upadacitinib, and abrocitinib may be sizable, it would be reasonable to expect patients to be tried on less costly off-label immunosuppressives before initiating the more expensive second-line agents.

All patients with atopic dermatitis treated with dupilumab, upadacitinib, or abrocitinib would be expected to continue on with emollients, TCSs, topical calcineurin inhibitors, and/or crisaborole. However, these 3 agents are not expected to be used in combination with the off-label systemic immunosuppressive drugs. Dupilumab is also not expected to be used in combination with upadacitinib or abrocitinib (or new biologics that are emerging in the treatment of atopic dermatitis).

Dupilumab, upadacitinib, and abrocitinib are unlikely to cause a significant shift in the current treatment paradigm for atopic dermatitis beyond their inclusion as additional effective treatment options in the armamentarium.

Upadacitinib or abrocitinib could also be of value for patients treated with dupilumab who have a suboptimal response, who develop severe conjunctivitis or other ocular side effects from dupilumab or are intolerant of injections and prefer an oral drug. Similarly, dupilumab could be of value for patients who experience suboptimal response to, or adverse effects with, JAK inhibitors.

### **Patient Population**

Any patient with moderate-to-severe atopic dermatitis could potentially benefit from treatment with dupilumab, upadacitinib, or abrocitinib. It is unclear whether these drugs can be used effectively in patients who have failed methotrexate and/or CSA. Efficacy of upadacitinib or abrocitinib in patients who have failed dupilumab, and vice versa, is also unclear.

It is not currently possible to predict those most likely to respond to dupilumab, upadacitinib, or abrocitinib.

### **Assessing Response to Treatment**

In general, the outcomes used in clinical practice are aligned with the outcomes typically used in clinical trials. The clinical expert consulted by CADTH anticipates that EASI score will be chosen as the benchmark for reimbursement. As such, this would generally be calculated and recorded at each patient visit. Many clinicians also record DLQI, although this value may not be required for reimbursement. Reduction in pruritus is also often noted but not formally scored using a scale. The patient's impression of their overall improvement would also be recorded.

Of these outcome measurements, a rational benchmark response will be a 75% reduction in EASI score from baseline values at 16 weeks. Achieving an EASI score improvement from baseline greater than or equal to 75% (EASI-75) with treatment would be clinically significant. Patients whose pruritus score is markedly

reduced and patients with severe disease recalcitrant to all previous therapies may find an EASI score reduction of 50% to 75% to be clinically meaningful.

Following initiation of dupilumab, it would be reasonable for patients to be re-evaluated at 24 weeks. A decision on whether to stop or continue therapy would be made at that 24-week visit. For patients treated with upadacitinib and abrocitinib, it would be reasonable for patients to be re-evaluated at 20 weeks following initiation of drug. A decision would be made at the 20-week visit whether to stop or continue.

The difference in maximum duration of initial reimbursement authorization (24 weeks [6 months] for dupilumab versus 20 weeks for upadacitinib and abrocitinib) is reasonable given the different mechanism of action and timing of onset of effect between interleukin inhibitors and JAK inhibitors.

### **Prescribing Conditions**

A specialist would be required to diagnose, treat, and monitor patients taking dupilumab, upadacitinib, or abrocitinib. Appropriate specialists would include a general dermatologist, pediatric dermatologist, allergist/immunologist, or pediatrician with experience and interest in atopic dermatitis. Restricting use to dermatologists and pediatric dermatologists only would ensure that all clinicians prescribing the 3 second-line systemic agents and monitoring for adverse events will have had experience in prescribing and monitoring the first-line systemic therapies in atopic dermatitis. However, given long wait lists and other barriers to accessing dermatologic consultative care, particularly in rural and remote locations in Canada, including additional specialists as prescribers would be expected to improve patient access and equity.

### **Additional Considerations**

Other potential off-label alternatives that could be used for atopic dermatitis (for example apremilast, retinoids, and ustekinumab) are unlikely to be prescribed in Canada for patients with atopic dermatitis and are therefore not relevant for the purpose of this review.

### **Harmonization of Reimbursement Conditions**

The clinical expert consulted by CADTH felt that alignment of the reimbursement conditions for dupilumab, upadacitinib, and abrocitinib is reasonable. Generally, all 3 agents are expected to be used as second-line systemic therapy after failure of or intolerance to systemic immunosuppressives in the treatment of atopic dermatitis. The specified prescribing specialists (general dermatologists, pediatric dermatologists, allergists/immunologists, or pediatricians with an interest in atopic dermatitis) should align for all 3 agents. However, it would be reasonable to continue with the original renewal criteria (duration of initial reimbursement), which differs between dupilumab and the 2 JAK inhibitors based on the different mechanism of action.

### **Clinician Group Input**

Input was received from 3 clinician groups, including the Canadian Dermatology Association, the Dermatologist and Allergist Group Managing Atopic Dermatitis, and Origins Dermatology Centre.

All clinician groups agreed with making some updates with respect to current reimbursement conditions recommended for dupilumab to align with those recommended for upadacitinib. A summary of points submitted by the clinician groups are as follows:

- 17 clinicians from the Dermatologist and Allergist Group Managing Atopic Dermatitis unanimously agreed that reimbursement conditions recommended for dupilumab should be aligned with those recommended for upadacitinib.
- Both the Canadian Dermatology Association and Origins Dermatology Centre agreed with revising 1 of the prescribing conditions recommended for dupilumab (“The patient must be under the care of a dermatologist”). They agreed with extending the authority from dermatologists only to specialists as listed in the prescribing condition recommended for upadacitinib (i.e., dermatologist, allergist, clinical immunologist, or pediatrician) with the rationale of ensuring equal and reasonable access to dupilumab.
- Origins Dermatology Centre agreed with updating the initiation condition recommended for dupilumab to include methotrexate, CSA, azathioprine, and mycophenolate mofetil, such that it aligns with the condition proposed for upadacitinib.

Conversely, the Canadian Dermatology Association did not agree with aligning current initiation criteria recommended for dupilumab with those recommended for upadacitinib. Instead, the Canadian Dermatology Association proposed several suggestions regarding how to revise the initiation criteria recommended for dupilumab based on a different place in therapy. As an alternative to these new recommendations, the Canadian Dermatology Association supported revising the dupilumab initiation condition such that it only requires failure of 1 of 4 systemic immunosuppressive therapies or prednisone. The Canadian Dermatology Association and Origins Dermatology Centre noted the differences in adverse effect profiles and monitoring required, some of which could be significant, as part of concerns with off-label use of systemic immunomodulators. Input from the Dermatologist and Allergist Group Managing Atopic Dermatitis also provided further suggestions, for example, adding other agents to the list of systemic immunomodulators for the patient to be treated with before initiating dupilumab, as well as extending the recommendation to include children aged 6 to 11 years. However, significantly altering the reimbursement conditions beyond aligning with upadacitinib and abrocitinib is out of the scope of this RfA. Details can be found in the full Stakeholder Input section at the end of this report.

### Manufacturer Input

Sanofi-Aventis Canada Inc. provided their perspective on updating the reimbursement conditions for dupilumab to align with those recommended for upadacitinib (and abrocitinib). Submitted input generally aligned with the clinical expert input, with an additional request included (#2 in the following list). In summary, the manufacturer provided the following input:

1. agrees and requests that the reimbursement condition for initiating dupilumab not be more restrictive upadacitinib or abrocitinib
2. requests that the condition for subsequent authorizations for dupilumab be revised to: “For subsequent renewal, the physician must provide proof of maintenance of EASI75 response from baseline every 12 months for subsequent authorizations.”

3. requests that the condition for prescribing for dupilumab be revised to: “The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.”

Of note, the manufacturer commented that while the reimbursement conditions for these agents may be aligned, they should not be identical because it is important to acknowledge the evidence and differences between them.

In its input, Sanofi-Aventis Canada Inc. noted that there is currently a disconnect in the reimbursement condition for initiation of dupilumab treatment regarding prior use of systemic immunosuppressant therapy. Concerns were raised regarding the lack of evidence of long-term safety and the potential for harms of requiring the use of systemic immunosuppressant therapy in patients with atopic dermatitis, and especially in children and adolescent patients, before allowing access to dupilumab. In particular, the manufacturer noted that reimbursement conditions places more restrictive criteria to dupilumab than other therapies in this space. The manufacturer noted that there is no evidence to support that the place in therapy for dupilumab is only after use of phototherapy (where available) and methotrexate and CSA, and emphasized that the recent CDEC recommendations for upadacitinib and abrocitinib, especially as they pertain to the conditions for initiation and prescribing, necessitate that the respective conditions of the CDEC recommendation for dupilumab be revised accordingly.

Sanofi-Aventis Canada Inc. concurred that it is reasonable to provide an initial authorization for a maximum of 6 months, as is currently recommended for dupilumab, to assess response to treatment and potential harms when initiating a patient. However, for subsequent renewal, the manufacturer requests an extension to 12 months based on available evidence, as well as increasing access by reducing follow-up appointments, given the lack of regular laboratory monitoring requirements, and to align with biologic agents used for other conditions, such as psoriasis.

For prescribing conditions, the manufacturer also concurred that the broader prescriber group, including dermatologists, allergists, clinical immunologists, and pediatricians who have expertise in the management of moderate to severe atopic dermatitis, are the most appropriate group to manage treatment with dupilumab.

Further details can be found in the full Stakeholder Input section at the end of this report.

## Possible Alignment of Criteria for CDEC Recommendations

Current CDEC recommendations and reimbursement conditions for dupilumab differ from those for upadacitinib and abrocitinib for the treatment of atopic dermatitis. Of the 3, dupilumab was reviewed first, and recommendations for upadacitinib (and subsequently abrocitinib) reflect more recent feedback received from drug plans participating in the CADTH reimbursement review process and clinicians.

In general, aligning reimbursement conditions between the 3 drugs was supported by the various stakeholders consulted for this RfA, as the patient population eligible for these 3 treatments would be

similar. There were some discrepancies between the CDEC recommendations and input from stakeholders (clinician groups, patient groups, and manufacturer of dupilumab), as well as the clinical expert, with regard to details on ideal reimbursement conditions for these treatments. However, there was overall consensus that, where appropriate and reasonable, the reimbursement conditions recommended for dupilumab should be updated to align with those recommended for upadacitinib and abrocitinib. To reduce implementation challenges that may be faced by the public drug plans, the information gathered suggests updating the following original reimbursement conditions for dupilumab:

- **Initiation criteria:**
  - Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.
  - Patients who have had an adequate trial of phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.
- **Prescribing conditions:**
  - The patient must be under the care of a dermatologist.

## Conclusion

Overall, the clinical expert and other stakeholders consulted by CADTH indicated that alignment of the reimbursement conditions for dupilumab, upadacitinib, and abrocitinib would be reasonable, in particular those that guide who will receive these drugs (initiation) and who would be able to prescribe these agents. As dupilumab would be expected to be prescribed similarly to the 2 JAK inhibitors, the information gathered in this RfA process suggests aligning the reimbursement conditions such that patients can access all 3 drugs following similar criteria if they are listed on public drug formularies for the treatment of atopic dermatitis.

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Dupilumab (Dupixent)

# Stakeholder Input

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## Patient Input

### Canadian Skin Patient Alliance and Eczéma Québec

**RE: Request for advice: Should the reimbursement conditions recommended for dupilumab (Dupixent) be updated to align with those recommended for upadacitinib (Rinvoq)?**

Dear Canadian Drug Expert Committee members:

The Canadian Skin Patient Alliance (CSPA) and Eczéma Québec (EQ) would like to acknowledge your initiative on reviewing the existing recommendation for dupilumab in light of the recently issued recommendation for upadacitinib. We appreciate the thoroughness of your review, as well as your consideration of our perspective on this issue.

#### Context

As you know, Atopic Dermatitis (AD) can have a profound impact on a person's wellbeing. Atopic dermatitis, commonly known as eczema, is the most common and burdensome skin disease worldwide, and affects up to 10% of adults and 20% of children in developed countries. AD is costly to both individuals and the healthcare system. In the United States alone, AD is estimated to cost from \$364 million to \$3.8 billion per year.

The disease manifests primarily as intense itching, excoriation (repeatedly picking at one's own skin), lichenification (thick and leathery skin), and skin discoloration. Debilitating itch, raw, bleeding skin, oozing sores, and superinfections are common and cause great discomfort, loss of sleep, and interruption of daily life, with resulting psychosocial comorbidities, including anxiety, depression, and feelings of isolation. AD is a complex disease to manage for both patients and clinicians due to its recurrent nature.

Furthermore, access to care and treatment for this patient population has been shown to be a challenge. With a nation-wide shortage of dermatologists and difficult accessibility to certain treatment options, many patients have to wait and suffer.

In the following sections of this document, we hope to discuss the existing recommendations for dupilumab and upadacitinib. We will then share our feedback in the context of the revision of the recommendation for dupilumab.

#### Review of Current Recommendations

In 2018, CADTH issued the final recommendation on the Atopic Dermatitis indication for dupilumab. This recommendation was superseded by the April 24, 2020, CADTH Canadian Drug Expert Committee Recommendation. (See recommendation in [Table 1](#))

In June of 2022, CADTH issued the CADTH Reimbursement Recommendation for upadacitinib. (See recommendation in [Table 1](#))

**Table 1: Comparative of Issued Recommendation for Dupilumab (April 2020) and Upadacitinib (June 2022)**

Comparator		Dupilumab (2020)	Upadacitinib (2022)
<b>Recommendation</b>		The CADTH Canadian Drug Expert Committee recommends that dupilumab should be reimbursed for the treatment of atopic dermatitis only if the following conditions are met.	CADTH recommends that Rinvoq be reimbursed by public drug plans for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe atopic dermatitis (AD) if certain conditions are met.
<b>Conditions for Reimbursement</b>	<b>Initiation criteria</b>	<ol style="list-style-type: none"> <li>1. Patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.</li> <li>2. Patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.</li> <li>3. Patients who have had an adequate trial phototherapy, methotrexate, and/or cyclosporine must have documented refractory disease or intolerance.</li> <li>4. The physician must provide the Eczema Area and Severity Index (EASI) score and Physician Global Assessment score at the time of initial request for reimbursement.</li> <li>5. The maximum duration of initial authorization is six months.</li> </ol>	<ol style="list-style-type: none"> <li>1. Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented intolerance), or are ineligible for each of the following therapies:               <ol style="list-style-type: none"> <li>1.1. maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and</li> <li>1.2. maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).</li> </ol> </li> <li>2. The physician must provide the EASI score and vIGA-AD score at the time of initial request for reimbursement.</li> </ol>
	<b>Renewal criteria</b>	<ol style="list-style-type: none"> <li>1. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI-75) six months after treatment initiation.</li> <li>2. The physician must provide proof of maintenance of EASI-75 response from baseline every six months for subsequent authorizations.</li> </ol>	<ol style="list-style-type: none"> <li>1. The maximum duration of initial authorization is 20 weeks. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a 75% or greater improvement from baseline in the EASI score (EASI75) 20 weeks after treatment initiation.</li> <li>2. For subsequent renewal, the physician must provide proof of maintenance of EASI 75 response from baseline every 6 months for subsequent authorizations.</li> </ol>
	<b>Prescribing conditions</b>	<ol style="list-style-type: none"> <li>1. The patient must be under the care of a dermatologist.</li> <li>2. Dupilumab is not to be used in</li> </ol>	<ol style="list-style-type: none"> <li>1. The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who</li> </ol>

Comparator		Dupilumab (2020)	Upadacitinib (2022)
		combination with phototherapy or immunosuppressant drugs, such as methotrexate or cyclosporine.	has expertise in the management of moderate to severe AD. 2. Upadacitinib should not be used in combination with phototherapy, any immunomodulatory drugs (including biologics) or other JAK inhibitor treatment for moderate to severe AD.
	Pricing	1. A reduction in price	1. A reduction in price

### Feedback for Revision of Dupilumab Recommendation

The CSPA, EQ and the MUHC-COE AD would like to propose the following update to the current recommendation for dupilumab:

#### *Recommendation*

That the general recommendation that dupilumab be reimbursed for the treatment of moderate to severe atopic dermatitis remains unchanged.

#### *Initiation criteria*

That the initiation criteria for dupilumab echo the upadacitinib initiation criteria.

#### *Renewal criteria*

That the renewal criteria remain as is with a maximum duration of initial authorization remains six months, reflecting the unique considerations for this product.

#### *Prescribing conditions*

That prescribing condition 1 be changed to echo the prescribing condition of upadacitinib:

The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.

#### *Pricing*

That the pricing criteria remain unchanged.

Additionally, we recognize that disease involvement in special sites (i.e., hands, face, nipples, genitalia) can represent a massive burden for patients, preventing them from engaging in work, leisure, or sexual activities. The existing recommendations do not currently include consideration for special sites involvement. However, in certain indications for psoriasis, the involvement of the disease on special sites such as the face or genitalia is considered as an important condition justifying reimbursement of a biologic if other criteria are not met. Concurrently, we would like to propose that involvement of special sites be included as part of the 'Initiation criteria' as an alternative to meeting criteria via overall severity.

### Conclusion

Our organisations are grateful for the mindfulness behind CADTH's reviews and updates to their recommendations. We hope to have provided feedback that will help inform the ongoing review of the



dupilumab recommendation for its indication in Atopic Dermatitis. Lastly, we wish to thank the CADTH review team for considering of our perspective on this matter.

### Canadian Skin Patient Alliance

**Did you receive help from outside your patient group to complete your feedback?**

Yes. The Canadian Skin Patient Alliance (CSPA) collaborated with Eczéma Québec, another patient organization supporting people with eczema in Quebec and affiliated with the McGill University Health Centre – Centre of Excellence in Atopic Dermatitis. The CSPA’s Executive Director also connected with the CEO of the Eczema Society of Canada to discuss perspectives while preparing the feedback.

**Did you receive help from outside your patient group to collect or analyze any information used in your feedback?**

Yes, see previous response.

**Were conflict of interest declarations provided in patient group input that was submitted as part of the initial CADTH review that the RfA is based on, and have those declarations remained unchanged?**

No

**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.**

**Table 2: New Financial Disclosures for Canadian Skin Patient Alliance**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Sanofi	–	–	–	X
AbbVie	–	–	–	X
Pfizer	–	–	–	X
LEO Pharma	–	–	X	–

### Eczéma Québec

**Did you receive help from outside your patient group to complete your feedback?**

Yes. Eczéma Québec collaborated with the Canadian Skin Patient Alliance (CSPA), another patient organization supporting people with eczema in Quebec and affiliated with the McGill University Health Centre – Centre of Excellence in Atopic Dermatitis. The CSPA’s Executive Director also connected with the CEO of the Eczema Society of Canada to discuss perspectives while preparing the feedback.

**Did you receive help from outside your patient group to collect or analyze any information used in your feedback?**

Yes, see previous response.

Were conflict of interest declarations provided in patient group input that was submitted as part of the initial CADTH review that the RfA is based on, and have those declarations remained unchanged?

No

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.

**Table 3: New Financial Disclosures for Eczéma Québec**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
AbbVie Canada	–	–	–	X
LEO Pharma	–	–	X	–
Sanofi Genzyme	–	–	–	X
Pfizer	–	–	–	X

**Eczema Society of Canada**

Thank you for reaching out to Eczema Society of Canada for the patient perspective on aligning reimbursement conditions for dupilumab (Dupixent) with those recommended for upadacitinib (Rinvoq).

The Eczema Society of Canada has contributed patient input submissions for dupilumab (Dupixent) and for upadacitinib (Rinvoq), along with a number of other novel therapies to treat moderate to severe atopic dermatitis.

While this is an exciting time of research and treatment breakthroughs for our patient community, these breakthroughs and new treatments mean little to patients if they cannot access these potentially life changing medications.

As you know from our input submissions, moderate to severe atopic dermatitis can be very challenging to manage and can have a significant quality of life impact on patients and caregivers.

Unfortunately, the patient experience here in Canada at this time, remains that novel systemic medications for atopic dermatitis can be very challenging if not impossible to access from a reimbursement perspective, and this varies greatly from province to province. Equitable and fair access to treatments - across disease states and across patient demographics - is desperately needed.

Requiring patients to fail multiple off-label medications before accessing the approved medications can be challenging, can pose significant barriers, and seems unreasonable and inequitable.

Moderate to severe AD can be challenging to manage for patients, caregivers, and health care providers. The criterion that a patient be under the care of specialists who have expertise in the management of moderate-to-severe AD and advanced therapies is reasonable.

Thank you for reaching out to us, and please contact us should you have any additional questions or require any additional information.

**Did you receive help from outside your patient group to complete your feedback?**

No.

**Did you receive help from outside your patient group to collect or analyze any information used in your feedback?**

No.

**Were conflict of interest declarations provided in patient group input that was submitted as part of the initial CADTH review that the RfA is based on, and have those declarations remained unchanged?**

Yes.

## Clinician Group Input

### Canadian Dermatology Association

Thank you for the opportunity to provide comment on whether the reimbursement conditions recommended for dupilumab (Dupixent) should be updated to align with those recommended for upadacitinib (Rinvoq).

The question has been considered by our Canadian Dermatology Association (CDA) Pharmacy and Therapeutics Expert Committee who have provided our recommendation and included additional recommendations for your consideration. Please find our response below:

#### Initiation Criteria

The CDA recommends that the initiation criteria for dupilumab not be aligned with the initiation criteria for upadacitinib, but rather it be aligned with the RAMQ criteria which provides reimbursement for patients aged 12 and over suffering from a moderate to severe form of chronic atopic dermatitis under the following conditions:

- in the presence of a score greater than or equal to 16 on the Eczema Area and Severity Index (EASI); and
- in the presence of a score greater than or equal to 8 on the Dermatology Life Quality Index (DLQI or cDLQI); and
- where 10% or more of the body surface area is affected; and
- where the disease is insufficiently controlled despite the use of topical treatments including at least two medium-or high-potency topical corticosteroids and one topical calcineurin inhibitor; and
- where a phototherapy treatment of 30 sessions or more during three months has not made it possible to optimally control the disease, unless this treatment is contraindicated, not tolerated or not accessible, or where a treatment of 12 sessions or more during one month has not provided significant improvement in the lesions.

### ***Rationale***

It is the CDA's unanimous position that biologic therapy is safer than targeted therapy and should be foremost in the assessment of the initiation criteria.

The four systemic immunomodulators mentioned in the initiation criteria - methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine – are not Health Canada-approved indications for the treatment of patients with moderate-to-severe atopic dermatitis.

Moreover, they have significant adverse effect profiles, far outweighing the limited data supporting their use in treating patients with atopic dermatitis. To date, there have been no incidences of lymphomas and venous thromboembolisms in patients receiving biologic therapies including dupilumab in comparison to targeted therapies (i.e., immunomodulators and JAK inhibitors).

Similarly, there are also lesser incidences of varicella-zoster virus and herpes simplex virus in patients receiving biologic therapies in comparison to targeted therapies, some of whom are just past their teen years in the latter group.

Our recommendation is also based on our interest to ensure equity for all Canadian patients and to spotlight the difficult position the current initiation criteria has placed on dermatologists.

The CDA recognizes and respects the outreach of CADTH's recommendations, however in this instance the initiation criteria is not equitable with the recommendations in Quebec. The differences are significant.

One requires a course of non-sanctioned immunosuppressants (i.e., methotrexate or cyclosporine) with potential risk for complications plus significant out-of-pocket costs for patients when the latter, a non-reimbursable medication not recommended for long-term use, is prescribed. While the other one is based on the presentation of the disease and the patient's response to a reasonable use of topical treatment options. As such, dermatologists are having to explain the multi-step criteria that does not put the patient's interests first.

It should also be acknowledged that other physician specialists may not have the same comfort level in prescribing these immunosuppressants.

With tens of thousands of Canadians having now received dupilumab under the existing initiation criteria, we are of the opinion there is sufficient evidence and clinical experience to support the revision of the initiation criteria and thereby allow physician specialists to prescribe dupilumab as a next step when topicals have failed.

If support for this recommendation is not possible, the initiation criteria for dupilumab should be revised to require only the failure of one of the four systemic immunosuppressive therapy options or prednisone.

### **Prescribing Criteria**

The CDA recommends that the prescribing criteria for dupilumab be revised to extend authority to allergists, clinical immunologists and pediatricians as listed for upadacitinib.



**Rationale**

In recognizing that some communities will not have a dermatologist practicing in close proximity, expanding the list of prescribers to other physician specialists who are qualified to diagnose and treat atopic dermatitis will ensure equal and reasonable access to this medication.

Thank you again for the opportunity to comment. The CDA would be pleased to provide further comment or explanation if needed at any time.

**Did you receive help from outside your clinician group to complete this submission?**

No

**Did you receive help from outside your clinician group to collect or analyze any information used in this submission?**

No.

**Were conflict of interest declarations provided in clinician group input that was submitted as part of the initial CADTH review that the RfA is based on, and have those declarations remained unchanged?**

No

**Declaration for Clinician 1**

**Name:** Susan Poelman, MD, FRCPC

**Position:** Chair, CDA Pharmacy and Therapeutics Committee

**Date:** 14-09-2022

**Table 4: COI Declaration for Canadian Dermatology Association – Clinician 1**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Abbvie	–	X	–	–
Sanofi Genzyme	X	–	–	–
Pfizer	X	–	–	–

**Declaration for Clinician 2**

**Name:** Maxwell Sauder, MD, FRCPC, DABD

**Position:** CDA Pharmacy and Therapeutics Committee Expert Advisor

**Date:** 18 Sep 2022

**Table 5: COI Declaration for Canadian Dermatology Association – Clinician 2**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Galderma Canada	–	–	X	–
Bausch Health	–	X	–	–
Sanofi	–	–	X	–
AbbVie	–	–	X	–
Pfizer	–	–	X	–
LEO	–	–	X	–
La Roche Posay	–	–	X	–
Amgen	–	–	X	–
Reystone Biopharma	–	–	X	–

**Declaration for Clinician 3**

**Name:** Michele Ramien, MD, FRCPC, DABD

**Position:** CDA Pharmacy and Therapeutics Committee Expert Advisor

**Date:** 23-09-2022

**Table 6: COI Declaration for Canadian Dermatology Association – Clinician 3**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Abbvie	–	–	X	–
Sanofi	–	–	X	–
Pfizer	–	–	X	–
Leo	–	–	X	–

**Declaration for Clinician 4**

**Name:** Yuka Asai, MD, FRCPC, DABD

**Position:** CDA Pharmacy and Therapeutics Committee Expert Advisor

**Date:** 25-09-2022

**Table 7: COI Declaration for Canadian Dermatology Association – Clinician 4**

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Sanofi	X	–	–	–
Pfizer	X	–	–	–
Leo	X	–	–	–
Abbvie	X	–	–	–
Sun Pharma	X	–	–	–
Eli Lilly	X	–	–	–
UCB	X	–	–	–
Kyowa Kirin	X	–	–	–
L’Oreal	X	–	–	–
Novartis	X	–	–	–
Medexus	X	–	–	–
Aralez	X	–	–	–
Canadian Society of Allergy and Clinical Immunology	X	–	–	–

**Origins Dermatology Centre, Regina, Saskatchewan**

**RE: Should the reimbursement conditions recommended for dupilumab (Dupixent) be updated to align with those recommended for upadacitinib (Rinvoq)?**

Thank you for considering my feedback RE: moderate to severe atopic dermatitis (AD)

I believe, and hope, from a clinician’s perspective that dupilumab reimbursement criteria should be updated to align with those proposed for upadacitinib. I believe that the updated criteria for upadacitinib (and hopefully dupilumab) is progressive in the Canadian context, for the following reasons:

1. Systemic immunosuppressant treatments for moderate to severe AD include Methotrexate, Cyclosporine, Azathioprine and Mycophenolate mofetil. As all are considered off-label immunosuppressants for moderate to severe AD in Canada, we should include them all (and they all come with similar potential side effect risk profiles and need for safety monitoring!)
2. Updated criteria will help to alleviate burdens on the prescribing dermatologist, as the primary prescriber and MRP (most responsible physician).
  - a) Comment: I think it is worth the committee noting that not all general/community dermatologists actively manage and prescribe potentially higher risk medications such as the traditional systemic immunosuppressants Methotrexate or Cyclosporine for moderate to severe inflammatory skin disease, and often refer out to other medical dermatologist colleagues who are experienced in prescribing and monitor/manage immunosuppressants for moderate to severe atopic dermatitis.

- b) Dermatologists generally face long wait times, and the majority are on fee for service. Dermatologist billing code income on the fee for service system are significantly less of that of general internal medicine (this is able to be seen through the initial consultation and follow-up codes in provincial physician payment schedules, such as those from Sask or Ontario). It is in my experience, as a medical based dermatologist in a critically underserved area (Saskatchewan), who prescribes and manages a significant amount of immunosuppressants, moderate to severe cases can be equally as impactful and burdensome similar to some complex internal medicine cases, and takes more time, resources, and effort in order to safely initiate and manage patients needing immunosuppression. Barriers may be present in underserved or rural areas such as lab or physician access or resources. It is not uncommon to see recurrent infections or side effects from these traditional immunosuppressants, in which we must monitor as the MRP and primary prescriber who take on the medicolegal risk of managing them. For examples of what types of burdens the traditional systemic immunosuppressants can create, please refer to product monographs. I have attached Methotrexate and Cyclosporine to this email as an example. Dermatologist overhead is generally high, immunosuppressants carry a paperwork and monitoring burden, and dermatologists can make more income, save time, and reduce medicolegal risk by focusing on more minor cases such as acne and warts (eg. we would make more income per patient, and save more time paring down a simple plantar wart, applying cryotherapy than we would managing multi-tiered needs of numerous, potentially comorbid patients needing systemic immunosuppression in an underserved health care system). Therefore, we must reduce the burdens on the already overburdened and under-resourced immunosuppressant prescribers for sake of advocating and supporting for medical dermatology sustainability for all generations of dermatologists.
3. I am an early career specialist, and do not fully understand the scope or implications of cost savings, but I respect that this also is a major and important consideration.
  4. Moderate to severe psoriasis, a chronic systemic inflammatory disease associated with numerous comorbidities and holistic impact, has already eliminated requirements to one immunosuppressant in many provinces.
  5. I believe that Allergist/Immunologist physicians and pediatricians also should be able to consider prescribing dupilumab and upadacitinib for moderate to severe AD, should it be within their level of scope of practice and experience.
  6. It is also worth noting that dupilumab does not require labwork, comes with a relatively good safety profile, and has drastically improved the life – physically, mentally, emotionally, functionally and financially of many AD sufferers and removed burdens off of prescribing dermatologists.

Thank you for your consideration.

**Did you receive help from outside your clinician group to complete this submission?**

No, I wrote this from my own personal clinical experience. In particular, in my experience, very few speak for rural, underserved, and Canadian Indigenous patients facing complex skin disease which is also why I am



hoping the group takes my feedback into consideration. I believe most input is from large urban centers that are much better serviced which my practice does not reflect.

**Did you receive help from outside your clinician group to collect or analyze any information used in this submission?**

No

**Were conflict of interest declarations provided in clinician group input that was submitted as part of the initial CADTH review(s) that the RfA is based on, and have those declarations remained unchanged?**

Yes

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

Dr. Rachel Asiniwasis

### **The Dermatologist and Allergist Group Managing Atopic Dermatitis**

The Dermatologist and Allergist Group Managing Atopic Dermatitis would like to thank CDEC/CADTH for the request to provide physician advice on dupilumab reimbursement conditions.

There was unanimous agreement that reimbursement conditions recommended for dupilumab should be updated to align with those recommended for upadacitinib.

Other suggestions proposed by the group for CDEC/CADTH considerations are:

- Add systemic steroids, JAK inhibitors and other approved biologic therapies for the treatment of moderate-to-severe AD to the list of systemic immunomodulators “maximally tolerated medical topical therapies for AD combined with at least one of the following systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, upadacitinib, abrocitinib, prednisone, or tralokinumab”
- Develop reimbursement criteria for children, age 6-11 in need of dupilumab therapy aligned with Health Canada approval “Dupilumab is indicated for the treatment of patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.”

I would like to thank my colleagues who provided input for this response (see below).

Please do not hesitate to request additional information or further physician input.

**Did you receive help from outside your clinician group to complete this submission?**

No.

**Did you receive help from outside your clinician group to collect or analyze any information used in this submission?**

No.

**Were conflict of interest declarations provided in clinician group input that was submitted as part of the initial CADTH review(s) that the RfA is based on, and have those declarations remained unchanged?**

Yes. Here is the list of clinicians who contributed input and whose declarations have not changed:

Dr. Irina Turchin, MD, FRCPC, DABD, Fredericton, NB

Dr. Kerri Purdy, Dermatology, Halifax, NS

Dr. Kirk Barber, Dermatology, Calgary, AB

Dr. Hermenio Lima, Dermatology and Allergy & Immunology, Burlington, ON

Dr. Sam Hanna, Dermatology, Toronto, ON

Dr. Wayne Gulliver, Dermatology, St. Johns, NFLD

Dr. Ashley Sutherland, Dermatology, Halifax, NS

Dr. Nicole Maillet-Lebel, Dermatology, Moncton, NB

Dr. Marni Wiseman, Dermatology, Winnipeg, MB

Dr. Ian Landells, Dermatology, St. Johns, NFLD

Dr. Gina Lacuesta, Allergy & Immunology, Halifax, NS

Dr. Lyne Giroux, Dermatology, Sudbury, ON

Dr. Stacey Northgrave, Dermatology, Sydney, NS

Dr. Sanjay Siddha, Dermatology, Toronto, ON

Dr. Marc Bourcier, Dermatology, Moncton, NB

Dr. Kamal Ohson, Dermatology, St. Johns, NFLD

Dr. Kim Papp, Dermatology, Waterloo, ON

## Manufacturer Input

### Sanofi-Aventis Canada Inc.

DUPIXENT® (dupilumab) is the first fully human monoclonal antibody targeted therapy indicated for the treatment of patients aged 6 years of age and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.<sup>1</sup> DUPIXENT has been evaluated in the largest clinical development program for AD to date in a broad patient population that spans adult patients ( $\geq 18$  years), adolescents ( $\geq 12$  to 17 years), and children ( $\geq 6$  years to 11 years) with moderate-to-severe AD. As part of the CADTH review of DUPIXENT for AD in adolescents and adults, the Canadian Drug Expert Committee (CDEC) considered 6 pivotal randomized

controlled trials (RCTs) (i.e., SOLO1, SOLO2, SOLO CONTINUE, LIBERTY AD CAFÉ, LIBERTY AD CHRONOS, and Study 1526). It has been shown that compared with placebo, treatment with DUPIXENT results in statistically and clinically significant improvements in a range of robust and validated AD outcomes encompassing disease severity and extent such as the Eczema Area and Severity Index (EASI), Investigator’s Global Assessment (IGA), and Scoring AD (SCORAD), intensity of itching by the Pruritus Numeric Rating Scale (NRS), AD symptoms by the Patient-Oriented Eczema Measure (POEM), anxiety and depression by the Hospital Anxiety and Depression Scale (HADS), and health-related quality of life by the Dermatology Life Quality Index (DLQI) and Children’s Dermatology Life Quality Index (CDLQI).<sup>2</sup> DUPIXENT has demonstrated long-term safety and tolerability in patients as young as 6 years with moderate-to-severe AD, as supported by data from clinical trials (up to 4 years)<sup>3</sup> and real-world evidence (up to 2 years)<sup>4</sup> and experience with over 450,000 patients treated worldwide. It is not an immunosuppressant and does not require routine laboratory monitoring. Taken together, the important treatment benefits of DUPIXENT were recognized by the CDEC in their positive recommendation to reimburse DUPIXENT for the treatment of AD with conditions.<sup>2</sup>

It is Sanofi’s position that the reimbursement conditions for DUPIXENT should reflect the Health Canada-approved indication and evidence from the dupilumab AD phase III clinical trial program. Reimbursement conditions must also take into consideration current Canadian clinical practice, input from clinical experts who treat AD and from patients who are living with AD and reflect the greatest unmet medical need which is the AD patient uncontrolled on topical therapy.

As more experience in this setting is gained and additional treatments for AD become available, it is important to revisit the reimbursement conditions for DUPIXENT in this context. To that end, while dupilumab (DUPIXENT), upadacitinib (RINVOQ), and abrocitinib (CIBINQO) are all indicated for the treatment of AD, their indications, posology, and evidence supporting their use in the most appropriate treatment population differs. Therefore, while the reimbursement conditions for these agents may be aligned, they should not be identical because it is important to acknowledge the evidence and important differences between them. DUPIXENT is approved as a first line systemic agent, whereas RINVOQ and CINIBQO are approved only as a second line systemic agent, as detailed in [Table 8](#).

**Table 8: Comparison of Health Canada Approved Systemic Treatments for Atopic Dermatitis**

Factor	Dupilumab (DUPIXENT)	Upadacitinib (RINVOQ)	Abrocitinib (CIBINQO)
Health Canada Approved Indication for AD	DUPIXENT (dupilumab injection) is indicated for the treatment of patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.	RINVOQ is indicated for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe AD who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable. RINVOQ can be used with or without topical corticosteroids.	CIBINQO (abrocitinib) is indicated for the treatment of patients 12 years and older with refractory moderate to severe AD, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable.

Factor	Dupilumab (DUPIXENT)	Upadacitinib (RINVOQ)	Abrocitinib (CIBINQO)
	DUPIXENT can be used with or without topical corticosteroids.		CIBINQO can be used with or without medicated topical therapies for AD.
<b>Mechanism of Action</b>	IL-4/IL-13 inhibitor	JAK1 inhibitor	JAK1 inhibitor
<b>Route of Administration</b>	SC injection	Oral	Oral
<b>Recommended Dose for AD</b>	Adults: 600 mg initial dose (2 x 300 mg), followed by 300 mg Q2W Children and Adolescents (6-17 years): BW-based dosing for ≥ 15 kg	Adults: 15 -30 mg once daily Adolescents (12-17 years): 15 mg once daily for ≥ 40 kg	Adults and Adolescents (12-17 years): 100 -200 mg once daily
<b>Limitations of Use</b>	None	RINVOQ should not be used in combination with other JAK inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as AZA and CsA.	Use of CIBINQO in combination with other JAK inhibitors, biologic immunomodulators, or potent immunosuppressants such as MTX and CsA has not been studied and is not recommended.

AD = atopic dermatitis; AZA = azathioprine; BW = body weight; CsA = cyclosporine; DMARD = disease modifying antirheumatic drug; IL = interleukin; JAK = Janus kinase; MTX = methotrexate; Q2W = every other week; SC = subcutaneous

Source: Dupixent Product Monograph<sup>1</sup>; Rinvoq Product Monograph<sup>5</sup>; Cibinqo Product Monograph<sup>6</sup>

The following responses and comments are organized according to the reimbursement conditions and reasons provided in the most recent CDEC recommendations for RINVOQ<sup>5</sup> and CIBINQO<sup>6</sup>:

### Initiation

As noted in the Request for Advice, there is currently a disconnect in the reimbursement condition for initiation of DUPIXENT treatment regarding prior use of systemic immunosuppressant therapy (IS) therapy. To meet the initiation condition for DUPIXENT, patients must have had an adequate trial or be ineligible for each of the following therapies: phototherapy (where available), methotrexate (MTX) and cyclosporine (CsA), whereas for RINVOQ and CIBINQO, patients must have had an inadequate response to only 1 of the 4 identified systemic IS therapies (i.e., MTX, CsA, mycophenolate mofetil [MMF], or azathioprine [AZA]).<sup>2,7,8</sup> The reason provided is that due to long-term safety concerns associated with IS therapy, input from the clinical expert, and practice assessments in other jurisdictions, it was reasonable to require that at least 1 conventional IS therapy be attempted prior to use of RINVOQ or CIBINQO.<sup>7,8</sup>

All DUPIXENT trials included a proportion of patients who had received at least 1 prior systemic IS (SIS) therapy. At baseline, the previous use of SIS was 28.4% in SOLO 1 and 2, 33.6% for CHRONOS and 20.8% in Study 1526. A post-hoc analysis of the SOLO1, SOLO2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ trials was conducted that included 503 patients who had previously received ≥ 1 systemic non-steroidal IS therapy.<sup>9</sup> In this analysis, all DUPIXENT-treated patients, regardless of concomitant topical corticosteroid (TCS) use or prior use of SIS therapy, achieved a significantly higher percentage reduction from baseline compared to placebo in EASI by Week 4, SCORAD, DLQI, and POEM by Week 2, a ≥ 3-point improvement in

Peak Pruritus NRS by Week 2, and  $\geq 4$ -point improvement by Week 3; DLQI score  $\leq 5$  by Week 2; and EASI score  $\leq 7$  and POEM score  $\leq 7$  by Week 4.<sup>9</sup>

Sanofi has repeatedly raised the concerns of the lack of evidence of long-term safety and the potential for harms by requiring the use of systemic IS therapy in patients with AD, and especially in children and adolescent patients, prior to allowing access to DUPIXENT. Moreover, many patients are not eligible for, or are contraindicated for IS therapy and importantly, none of the identified IS therapies (i.e., MTX, CsA, MMF, or AZA) are approved by Health Canada for use in the treatment of AD. The current restriction of DUPIXENT to patients who have failed or are ineligible for phototherapy, MTX, and CsA denies a vulnerable patient population with high unmet need access to an effective and safe treatment. Moreover, it unfairly places more restrictive conditions on DUPIXENT, which is the treatment with the largest body of evidence supporting its efficacy and safety in a broad population of patients with AD, as compared with RINVOQ and CIBINQO, namely the uncontrolled post topical AD population. Recent experience with the implementation of the current DUPIXENT public reimbursement criteria is that the requirement of a trial of MTX and CSA has been challenging to meet for many patients and the reasons of contraindication and ineligibility are not often accepted. Physicians have provided feedback that many do not prescribe immunosuppressants, especially in adolescents, and that it is not common for 2 immunosuppressants to be prescribed due to their safety profile, interactions, and intolerance.

In response to the Request for Advice, Sanofi agrees and requests that the reimbursement condition for initiating DUPIXENT **not be more restrictive** RINVOQ or CIBINQO, that is, “Patients must have had an adequate trial (with a documented refractory disease), or were intolerant (with documented intolerance), or are ineligible for each of the following therapies: 1.1) maximally tolerated medical topical therapies for AD combined with phototherapy (where available), and 1.2) maximally tolerated medical topical therapies for AD combined with at least 1 of the 4 systemic immunomodulators (methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine).”

In addition, CDEC recommended DUPIXENT be reimbursed for “patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable”. This is aligned to the Health Canada indication and should remain unchanged in the DUPIXENT initiation criteria. CDEC also recommended DUPIXENT be reimbursed for “patients who have had an inadequate trial of phototherapy (where available), MTX and CsA”. To be no more restrictive with the RINVOQ and CIBINQO criteria, DUPIXENT should require a trial of only one systemic immunosuppressant (i.e., MTX or CsA). For clarity, MTX, CsA, MMF and AZA are classified as immunosuppressants.

Despite the criteria for RINVOQ and CIBINQO and their documented safety concerns, based on the Health Canada-approved indication, clinical trial evidence, evolving Canadian clinical practice, reimbursement by RAMQ and private insurers, longer-term and real world evidence of safety and efficacy, public reimbursement for DUPIXENT should be considered for patients with moderate-to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

## Renewal

Sanofi concurs that it is reasonable to provide an initial authorization for a maximum of 6 months, as is currently recommended for DUPIXENT, to assess response to treatment and potential harms when initiating a patient. As more experience with DUPIXENT maintenance therapy has now been gained, it would be reasonable to extend the maximum duration of subsequent authorizations to 12 months rather than 6 months. This is supported by evidence of long-term safety and efficacy of DUPIXENT in the LIBERTY AD CHRONOS trial where EASI75 was maintained from baseline over 52 weeks.

Both the RINVOQ and CIBINQO product monograph indicate response evaluation is required and regular laboratory monitoring is required. There are no such requirements with DUPIXENT therapy further supporting an increase to the renewal authorization to at least 12 months.

Access to dermatologists and other specialists who treat AD is extremely limited, which compromises the ability for both patients and physicians to meet the requirement for ongoing 6-month assessments for the purpose of renewing coverage for DUPIXENT. Of note, the requirement for 6-month renewals is also more restrictive than is currently in place for other biologic agents used for the treatment of dermatologic conditions such as psoriasis which allows for 12-month subsequent renewal criteria.

In response, Sanofi requests that the condition for subsequent authorizations for DUPIXENT be revised to **“For subsequent renewal, the physician must provide proof of maintenance of EASI75 response from baseline every 12 months for subsequent authorizations.”**

## Prescribing

AD is a chronic disease that is diagnosed and managed by various healthcare professionals, as acknowledged by CDEC in the RINVOQ and CIBINQO recommendations.<sup>7,8</sup> Both the Canadian Pediatric and Adult AD Consensus Statements were co-authored by dermatologists and allergists, reflecting the joint management of AD.<sup>10,11</sup> Moreover, the Pediatric AD Consensus Statement specifically states that physicians treating pediatric patients with AD includes dermatologists, pediatricians, allergists, and other healthcare professionals.<sup>11</sup> Allergists are particularly important in the treatment of AD in pediatric patients as they are often the first point of contact for patients with AD as access to dermatologists typically takes much longer. Moreover, the Health Canada approved indication for DUPIXENT (as well as those of RINVOQ and CIBINQO) do not limit prescribing to a specialist or a particular specialty.<sup>1,5,6</sup> Given the favorable safety profile of DUPIXENT compared with RINVOQ and CIBINQO, the broader prescriber group, including dermatologists, allergists, clinical immunologists, and pediatricians who have expertise in the management of moderate to severe AD, are the most appropriate group to manage treatment with DUPIXENT.

In response, Sanofi requests that the condition for prescribing for DUPIXENT be revised to **“The patient must be under the care of a dermatologist, allergist, clinical immunologist, or pediatrician who has expertise in the management of moderate to severe AD.”**

Patients with AD who are candidates for systemic therapy and who have had an inadequate response to, are intolerant of, or ineligible for IS therapy suffer a high disease burden and reflect a patient population with high unmet need. There is no evidence to support that the place in therapy for DUPIXENT is only after use

of phototherapy (where available) and MTX and CsA and in fact the evidence is to the contrary. The recent CDEC recommendations for RINVOQ and CIBINQO, especially as they pertain to the conditions for initiation and prescribing, necessitates that the respective conditions of the CDEC recommendation for DUPIXENT be revised accordingly. The current conditions for reimbursement of DUPIXENT, which are more restrictive than those of RINVOQ and CIBINQO, unfairly restricts access to the one treatment with the largest body of evidence in support of its efficacy and safety across a broad population of patients comprising adults, adolescents, and children with inadequately controlled moderate-to-severe AD.

## References

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