

# Drug Coverage Decision for B.C. PharmaCare

## About PharmaCare

B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

## Details of Drug Reviewed

<b>Drug</b>	<b>mycophenolate mofetil</b>
Brand Name	Teva-Mycophenolate
Dosage Forms	250 mg capsule, 500 mg tablet
<b>Submission Type</b>	Ministry Initiated
Use Reviewed	Bullous Pemphigoid and Autoimmune Hepatitis
Common Drug Review (CDR)	No, CDR did not review
Drug Benefit Council (DBC)	<p>DBC met on March 4, 2019.</p> <p><u>Bullous Pemphigoid</u>: In their review, the DBC considered a <i>Systematic Literature Review of the beneficial and harmful effects of Mycophenolate Mofetil used for Bullous Pemphigoid</i>, a Clinical Practice Review from a specialist, and a Budget Impact Assessment. The DBC received no Patient Input Questionnaires in response to the request for submissions.</p> <p><u>Autoimmune Hepatitis</u>: In their review, the DBC considered various inputs including: a <i>Systematic Literature Review of the beneficial and harmful effects of Mycophenolate Mofetil used for Autoimmune Hepatitis</i>, a Clinical Practice Review from a specialist, and a Budget Impact Assessment. The DBC received no Patient Input Questionnaires in response to the request for submissions.</p>
<b>Drug Coverage Decision</b>	<b>Limited Coverage Benefit. Access the mycophenolate mofetil criteria from <a href="http://www.gov.bc.ca/pharmacarespecialauthority">www.gov.bc.ca/pharmacarespecialauthority</a></b>
Date	November 26, 2019
Reason(s)	<p><b>Drug coverage decision is consistent with the DBC recommendation.</b></p> <ul style="list-style-type: none"> <li>• DBC recommended to fund mycophenolate for the two indications based on clinical evidence.</li> <li>• The drug was similar to its comparators with respect to efficacy, and safety. Based on economic considerations and the submitted product price, the drug was cost effective and offered value for money.</li> </ul>
Other Information	The Ministry provides coverage to mycophenolate on exceptional case by case basis. This review was initiated as generic mycophenolate is available at a substantially lower cost if coverage is provided through a public drug plan.

### The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the [Drug Benefit Council \(DBC\)](#) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the [Common Drug Review \(CDR\)](#)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit [The Drug Review Process in B.C. - Overview](#) and [Ministry of Health - PharmaCare](#) for more information.

**This document is intended for information only.**

It does not take the place of advice from a physician or other qualified health care provider.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Mycophenolate mofetil (CellCept®)

Hoffmann-La Roche Ltd.

Description:

Drug review of mycophenolate mofetil (CellCept®) for the following indications:

For the treatment of bullous pemphigoid in patients who have already tried oral/systemic high potency corticosteroids or for whom high potency corticosteroids are contraindicated due to other comorbidities.

Oral mycophenolate is available in two different formulations: mycophenolate mofetil (CellCept) and enteric-coated mycophenolate sodium (Myfortic®). These formulations have different characteristics and should not be used interchangeably.

Mycophenolate mofetil (CellCept) has the following Health Canada approved indications:

- Adults: the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.
- Pediatrics (2-18 years of age): the prophylaxis of organ rejection in pediatric patients (2 to 18 years) receiving allogeneic renal transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CellCept has been used off-label for many serious auto-immune conditions, including: autoimmune hepatitis, bullous pemphigoid, lupus nephritis, myasthenia gravis, psoriasis; and systemic sclerosis.

Under its approved indications CellCept is not an eligible PharmaCare benefit. The Ministry of Health is evaluating alternative PharmaCare listing options.

In their review, the DBC considered a Systematic Literature Review of the Beneficial and Harmful Effects of Mycophenolate Mofetil used for Bullous Pemphigoid. The DBC also considered Clinical Practice Reviews from two specialists and a Budget Impact Assessment. The DBC received no Patient Input Questionnaires in response to the request for submissions.

#### Dosage Forms:

CellCept® is available as mycophenolate mofetil 500 mg tablet, 250 mg capsule, and 200 mg/mL solution.

#### Recommendations:

1. The Drug Benefit Council (DBC) recommends that mycophenolate mofetil (CellCept®) be listed as a Limited Coverage benefit for treatment of bullous pemphigoid.
2. Limited coverage criteria should be determined in consultation with dermatology experts. Mycophenolate mofetil should be used after azathioprine.

#### Reasons for the Recommendation:

##### 1. Summary

- One randomized controlled trial (RCT) reported that more patients with bullous pemphigoid in the mycophenolate mofetil group experienced complete healing of lesions and disease remission than in the azathioprine group. Both mycophenolate mofetil and azathioprine were similarly efficacious in the length of disease-free survival.
- Mycophenolate mofetil was associated with a significantly lower toxicity profile than azathioprine with respect to abnormal liver function.
- Listing CellCept as a Limited Coverage benefit would incur a moderate budget impact to PharmaCare.

##### 2. Clinical Efficacy

- The DBC considered the systematic review, which identified one randomized controlled trial (RCT) that met the inclusion criteria. Beisert 2007 was a multicenter, randomized, non-blinded clinical trial conducted in Germany that enrolled patients with bullous pemphigoid who were on average 75.3 years old with a minority of patients who had received prior treatment. The trial compared two parallel groups of patients with bullous pemphigoid that were treated with oral methylprednisolone (0.5 mg/kg) in combination with either azathioprine (2mg/kg once daily), or mycophenolate mofetil (2g/day). Patients were randomized to receive either methylprednisolone plus azathioprine or methylprednisolone plus mycophenolate mofetil.
- The trial reported that complete healing of lesions and disease remission was achieved in all patients taking mycophenolate mofetil and was non-inferior to azathioprine, and that more patients with bullous pemphigoid in the mycophenolate mofetil group experienced complete healing of lesions and disease remission than in the azathioprine group. However, both mycophenolate mofetil and azathioprine were similarly efficacious in the length of disease-free survival.
- The population in the trial included patients with and without prior treatment, which may affect the generalizability of the results to adult patients with bullous pemphigoid who have previously failed on oral/systemic high potency corticosteroids or for whom high potency corticosteroids are contraindicated due to other comorbidities.

### 3. Safety

- Mycophenolate mofetil was associated with a significantly lower toxicity profile than azathioprine with respect to abnormal liver function.

### 4. Economic Considerations

- At a cost of approximately \$12,000 per patient for a two-year course of therapy at the recommended dosage, CellCept is significantly more expensive than other drugs also used to treat bullous pemphigoid, namely azathioprine (approximately \$2,242 for three years) and methylprednisolone (approximately \$3,285 for two years). The response to these drugs is dependent upon the patient and may be highly variable.
- There is a small number potential number of patients who have already tried oral/systemic high potency corticosteroids or for whom high potency corticosteroids are contraindicated.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Mycophenolate mofetil (CellCept®)

Hoffmann-La Roche Ltd.

Description:

Drug review of mycophenolate mofetil (CellCept®) for the following indications:

For the treatment of autoimmune hepatitis (AIH) in patients who have had an inadequate response to combination therapy of prednisone or budesonide and azathioprine or for whom long-term use of glucocorticoids is contraindicated due to other comorbidities such as diabetes, osteoporosis, history of psychosis or poorly controlled hypertension.

Oral mycophenolate is available in two different formulations: mycophenolate mofetil (CellCept) and enteric-coated mycophenolate sodium (Myfortic®). These formulations have different characteristics and should not be used interchangeably.

Mycophenolate mofetil (CellCept) has the following Health Canada approved indications:

- Adults: the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.
- Pediatrics (2-18 years of age): the prophylaxis of organ rejection in pediatric patients (2 to 18 years) receiving allogeneic renal transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CellCept has been used off-label for many serious auto-immune conditions, including: autoimmune hepatitis, bullous pemphigoid, lupus nephritis, myasthenia gravis, psoriasis; and systemic sclerosis.

Under its approved indications CellCept is not an eligible PharmaCare benefit. The Ministry of Health is evaluating alternative PharmaCare listing options.

In their review, the DBC considered a Systematic Literature Review of the beneficial and harmful effects of Mycophenolate Mofetil used for Autoimmune Hepatitis, a Clinical Practice Review from a specialist, and a Budget Impact Assessment. The DBC received no Patient Input Questionnaires in response to the request for submissions.

#### Dosage Forms:

CellCept® is available as mycophenolate mofetil 500 mg tablet, 250 mg capsule, and 200 mg/mL solution.

#### Recommendations:

1. The Drug Benefit Council (DBC) recommends that mycophenolate mofetil (CellCept®) be listed as a Limited Coverage benefit for treatment of autoimmune hepatitis.

#### Of Note:

- Limited Coverage criteria should be determined in consultation with hepatology experts.

#### Reasons for the Recommendation:

##### 1. Summary

- A systematic review that included nine observation and non-randomized studies reported that in nearly half of the included studies mycophenolate mofetil was more effective for inducing remission or complete response in patients who were intolerant to previous treatment, as compared to patients who were non-responsive to previous treatment.
- Among the studies that examined harms-related outcomes, mycophenolate mofetil was either a safe alternative for the treatment of AIH in both adult and pediatric populations or it was well tolerated in study populations.
- Listing CellCept as a Limited Coverage benefit would incur a moderate budget impact to PharmaCare.

##### 2. Clinical Efficacy

- The DBC considered the systematic review, which found a total of nine studies that met the pre-defined inclusion criteria.
- Among the eight studies that addressed the efficacy of mycophenolate mofetil in adult patients with AIH, nearly half of the included studies found that mycophenolate mofetil was more effective for inducing remission or complete response in patients who were intolerant to previous treatment, as compared to patients who were non-responsive to previous treatment.
- One study found mycophenolate mofetil to be similarly effective for both patients who had suboptimal response to standard therapy and those who were intolerant of standard therapy.
- Two studies did not stratify patients according to their response to prior treatment and found that a majority of patients achieved remission on mycophenolate mofetil, and that mycophenolate mofetil monotherapy induced a higher percentage of remission compared to tacrolimus or mycophenolate mofetil plus tacrolimus.
- One study found that none of the patients taking mycophenolate mofetil achieved remission, although a majority did achieve a response to treatment.
- The single pediatric-only study found that mycophenolate mofetil was more effective for inducing remission in patients who were intolerant to prior treatment, as compared to those who were non-responsive to prior treatment.
- The included studies were observational and non-randomized and are subject to a higher risk of bias compared to randomized controlled trials. Two of the studies may present duplicate pediatric data, however this duplication cannot be confirmed based on the reported information in both studies.
- While the majority of patients included in the eight studies were adults, three studies introduced potential bias by including a small proportion of pediatric patients into the overall study population and not controlling for any potential effects.
- Further limitations identified during the critical appraisal process included small sample sizes, varied follow-up times, varied outcomes definitions, and a few studies did not control for switching to mycophenolate mofetil treatment. Finally, only one study with an entirely pediatric population was identified and thus the generalizability of these findings is limited.

### 3. Safety

- Among the seven studies that examined harms-related outcomes, the majority found that treatment with mycophenolate mofetil was either a safe alternative for the treatment of AIH in both adult and pediatric populations or that it was well tolerated in study populations. The most commonly reported side effects were gastrointestinal symptoms.

### 4. Economic Considerations

- At a cost of approximately \$12,000 per patient for a two-year course of therapy at the recommended dosage, CellCept is significantly more expensive than other drugs also used to treat AIH, namely tacrolimus (approximately \$367 for six months) and azathioprine (approximately \$214).
- There is a small number potential number of patients who have had an inadequate response to other therapies or for whom long-term use of glucocorticoids is contraindicated.