BEHCET DISEASE

CHI Formulary Indication Review

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Abbreviations

5-ASA	5-Aminosalicylic Acid
ANB	Acute Neuro-Behcet's Disease
ASHP	American Society of Health-System Pharmacists
AST/ALT	Aspartate Aminotransferase/Alanine Aminotransferase
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin
BCS	Budd-Chiari Syndrome
BD	Behcet Disease
BS	Behcet Syndrome
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHI	Council of Health Insurance
CNS	Central Nervous System
CPNB	Chronic Progressive Neuro-Behcet's disease
CRRT	Continuous Renal Replacement Therapy
CsA	Cyclosporine A
CSF	Cerebrospinal Fluid
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FDA	U.S. Food and Drug Administration
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IM	Intramuscular
IL-6	Interleukin-6
IV	Intravenous
KSA	Kingdom of Saudi Arabia
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NB	Neuro-Behcet's Disease
NSAID	Nonsteroidal Anti-Inflammatory Drug
PIRRT	Prolonged Intermittent Renal Replacement Therapy
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PO	Per Os (Orally)
RCT	Randomized Controlled Trial
SFDA	Saudi Food and Drug Authority
SQ	Subcutaneous
TB	Tuberculosis
TNF	Tumor Necrosis Factor

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Executive Summary

Behçet's disease (BD), also known as Behçet syndrome, is a rare autoimmune disorder that causes inflammation in blood vessels throughout the body. It was named after the Turkish dermatologist Hulusi Behçet, who first described the disease in 1937. It is a rare inflammatory disorder that affects multiple systems in the body and is characterized by the presence of ulcers in the mouth and genital region, various skin lesions, and eye abnormalities. Symptoms include mucous membrane lesions in the form of canker sores in the mouth and ulcers in the genital area, exhibiting a pattern of spontaneous disappearance and recurrence. This syndrome can impact additional bodily systems, including the joints, blood vessels, central nervous system, and digestive tract. Despite ongoing research, the precise cause of Behçet's syndrome remains unknown[1].

Behçet's syndrome presents with initial symptoms such as painful canker sores in the mouth, often recurring and healing without scarring. Genital sores may also occur, potentially leading to scarring. Eye involvement includes inflammation of the back or front of the eye, potentially causing vision issues or blindness with repeated occurrences. Skin manifestations include pustules, lesions resembling erythema nodosum, acneiform eruptions, and pseudofolliculitis. Joint pain and swelling, affecting knees, wrists, elbows, and ankles, may occur in about half of cases, with lasting joint damage being rare. Recurring ulcers in the digestive tract can cause abdominal discomfort or severe inflammation. Central nervous system involvement is seen in 10%-20% of cases, causing neurological damage and symptoms such as headaches, ataxia, pseudobulbar palsies, strokes, meningitis, and seizures. Behçet's syndrome also involves vasculitis, potentially affecting small vessels, large veins, and arteries, leading to aneurysms or thrombophlebitis. Kidney and peripheral nerve involvement is rare. Recognition of BD is crucial, especially in cases with ocular, central nervous system, or large blood vessel involvement, as these manifestations are typically the most serious[1].

The exact cause of Behçet’s syndrome remains elusive. Research indicates a potential genetic predisposition, implying that certain individuals may carry a gene associated with the condition, but its expression may require environmental triggers. Studies show an increased frequency of specific human leukocyte antigens (HLAs) in individuals with Behçet’s syndrome, particularly those of Middle Eastern and Asian descent, with HLA-B51 being more prevalent than in the general population. The exact role of HLA-B51 in predisposing individuals to Behçet’s syndrome is not fully understood, and ongoing research is exploring other genetic markers. Additionally, viral or bacterial infections have been proposed as potential contributors to the disorder. Another theory suggests Behçet’s syndrome may be an auto-inflammatory disorder, where the body loses its ability to regulate inflammation appropriately.

Autoimmune disorders arise when the body's natural defenses, such as antibodies, mistakenly target healthy tissues without a clear cause. Despite ongoing investigations, no autoantibodies have been identified thus far to categorize Behçet's syndrome as a definitive autoimmune disease[1].

In addition to an elevated risk of mortality, Behçet's disease is linked to various potential lifelong complications, largely stemming from ocular or neurologic implications. Individuals with hypopyon-related uveitis and retinal involvement face a significant risk of blindness. Behçet's disease is also associated with the rupture of coronary or pulmonary arterial aneurysms, posing a considerable threat to life[1].

In cases of central nervous system involvement, the potential consequences include substantial morbidity, lasting deficits, and even mortality. Ocular complications, such as anterior and posterior uveitis, can lead to enduring blindness. Furthermore, another complication associated with Behçet's disease is an increased likelihood of miscarriages, attributed to placental vasculitis[2].

Behçet's syndrome is a rare disorder in the United States and Western Europe. It occurs most frequently in the Middle East and Asia, along ancient trading routes between the Mediterranean basin and eastern Asia, known as the Silk Road. Turkey has the highest prevalence rate; Japan, Korea, China, Iran, and Saudi Arabia also have high prevalence rates. The disorder is the leading cause of blindness in Japan. The age of onset is typically between 30 and 40 years. Epidemiological reports have confirmed that the Levant and the Middle East lie at the global epicenter of BD, with prevalence ranging up to 240 per 100 000 population in Turkey. However, over the last 50 years, BD has been more widely recognized worldwide. In Western Europe, prevalence has been reported at 7.5, 7.1 and 1.1 per 100 000 population in Spain, France, and Germany, respectively. In comparison, there have been relatively few attempts at estimating the prevalence of BD within the UK. The most recent estimates come from over 20 years ago and range from 0.27 to 0.64 per 100 000 population. In the United States, the estimated prevalence ranges from 0.33 to 5.2 people per 100,000 population. The prevalence of BD in the U.S. is increasing, which may be due to increased disease recognition and immigration from endemic areas; however, robust epidemiologic data about BD in the U.S. is scarce[1,3,4].

Despite two prior cohort studies from Saudi Arabia revealing no notable distinctions in clinical manifestation or prognosis between male and female patients with BD, comprehensive studies addressing the incidence and prevalence of the disease have been lacking, even after decades of disease recognition for this country. Consequently, studies are needed to examine and delineate the clinical features and characteristics of individuals diagnosed with BD in Saudi Arabia[5].

The burden of disease associated with BD includes various factors such as pain, discomfort, healthcare costs, and potential complications. The disease burden associated with Behçet syndrome typically occurs primarily in the initial years of its

progression, and in many patients, the syndrome undergoes a period of reduced activity. Nevertheless, exceptions exist, particularly in cases involving central nervous system participation and significant vessel disease, which may manifest late in the course of the illness, typically 5 to 10 years after onset. Mortality data indicates that, across various disease manifestations, the impact of the syndrome was generally less severe in females. Notably, no female patients were identified with arterial aneurysms. A cost analysis study of Behcet's syndrome in Turkey published in 2007 showed that the mean annual total cost per patient amounted to US$ 3226 +/- 3488 (standard deviation). Direct costs constituted 68% of the total expenditure, with medication expenses representing 79% of the overall direct costs. Approximately 42% of patients reported experiencing lost workdays, with an average of 119 +/- 96 days (standard deviation). When considering clinical subgroups, mucocutaneous-joint involvement had the least economic impact, totaling US$ 1180 +/- 1053, while neurological disease exhibited the highest economic impact at US$ 5005 +/- 2707[6,7].

This report compiles all clinical and economic evidence related to Behcet Disease according to the relevant sources. The ultimate objective of issuing Behcet Disease guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to Behcet Disease patients in Saudi Arabia**. The main focus of the review was on **North American** and **joint European** and other **international guidelines** issued within the last five years. To elaborate, **North American guidelines** detailed the management of Behcet Disease with the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Furthermore, **European and International guidelines** elaborated recommendations for the management of Behçet's syndrome while focusing on each aspect of disease management: ocular manifestations, vascular skin/mucosal and intestinal manifestations. In addition, a **recent systematic review and meta-analysis** was tackled; thereby providing an in-depth understanding of the efficacy and safety of anti-tumor necrosis factor agents in the treatment of intestinal Behcet's disease. An additional systematic review and meta-analysis was added and discussed the updates of EULAR recommendations for the Management of major organ involvement of Behcet's syndrome.

Drug therapy is an integral component for the management of Behçet disease. The goals of treatment of Behçet disease include symptom control (reducing inflammation and pain management), prevention of complications, maintenance of functionality (joint function and central nervous system function), improving quality of life and long-term disease management. Treatment for Behçet's syndrome is tailored to address the specific symptoms present in each individual. Therapies are primarily symptomatic and supportive. Factors such as the severity of the condition, the patient's age, and gender influence treatment decisions. Many individuals with Behçet's syndrome experience spontaneous remission over time.

- For oral and genital ulcerations, corticosteroid-containing preparations applied topically may help abort developing attacks. Mouthwash with a local anesthetic like lidocaine or diphenhydramine can temporarily alleviate pain. Colchicine is effective in preventing recurrent attacks, and Apremilast is FDA-approved for recurrent oral ulcers. More aggressive therapies, including azathioprine, thalidomide, interferon-alpha, and anti-TNF agents, may be considered.
- Arthritis associated with Behçet's may respond to nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. Azathioprine and anti-TNF agents are options for more aggressive or refractory disease.
- Collaboration with an ophthalmologist is crucial for treating eye inflammation. Corticosteroid eye drops may relieve pain, and for more severe cases, oral corticosteroids combined with azathioprine or anti-TNF agents are used.
- Inflammatory bowel disease and gastrointestinal lesions associated with Behçet's may be treated with sulfasalazine, azathioprine, and corticosteroids. Central nervous system and vascular abnormalities may be addressed with corticosteroids, often combined with immunosuppressive agents. In cases of clotting in major blood vessels, systemic anticoagulants and immunosuppressants should be considered.
- Oral corticosteroids can reduce inflammation in joints, skin, mucous membranes, or other organs. However, they do not prevent recurring symptoms and may not reduce damage alone. Immunosuppressive agents like azathioprine, methotrexate, cyclosporine, or chlorambucil may be used for better inflammation control and organ protection. Ongoing research explores the use of interferon-alpha and agents inhibiting tumor necrosis factor (TNF) in Behçet's disease treatment[1].

Main recommendations issued by different health technology assessment (HTA) bodies on the use of the current medications in Behcet Disease were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines and Strength of Agreement (SoA) reflecting the specific drug class role in the management of Behcet Disease.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. SFDA-Registered Drugs Used in the Management of Behcet Disease

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Colchicine	Mucocutanous involvement of Behcet Disease	**1st**	IB, A[8]	No HTA Recommendations were issued by the concerned HTA bodies.
	Joint involvement of Behcet Disease		IB, A[8]	
Prednisone	Mucocutanous involvement of Behcet Disease	**1st**	IB, A[8] Evidence level: 5, Grade of recommendation: C1[9]	No HTA Recommendations were issued by the concerned HTA bodies.
	Ocular manifestations of Behcet Disease		Not graded[10]	
	Thrombosis manifestations of Behcet Disease		Not graded[10] Evidence level: 3, Grade of recommendation: C1[9]	
	Joint involvement of Behcet Disease		Not graded[11]	
	Gastro-intestinal Behcet Syndrome		Evidence level: 5, Recommendation: A[9]	
Methylprednisolone	Mucocutanous involvement of Behcet Disease	**1st**	IB, A[8] Evidence level: 5, Grade of recommendation: C1[9]	No HTA Recommendations were issued by the concerned HTA bodies.
	Ocular manifestations of Behcet Disease		Not graded[10]	

	Thrombosis manifestations of Behcet Disease		Not graded[10] Evidence level: 3, Grade of recommendation: C1[9]	
	Joint involvement of Behcet Disease		Not graded[11]	
	Gastro-intestinal Behcet Syndrome		Evidence level: 5, Recommendation: A[9]	
Adalimumab	Ocular manifestations of Behcet Disease	**2nd**	Strong recommendation, moderate quality of evidence[12]	**NICE:** Conditional Positive Recommendation[13] **HAS:** Positive Recommendation[14]
	Joint manifestations of Behcet Disease		Strong recommendation, good quality of evidence[12]	
Azathioprine	Mucocutanous involvement of Behcet Disease	**2nd (recurrent/ chronic cases)**	IB, A[8]	No HTA Recommendations were issued by the concerned HTA bodies.
	Ocular manifestations of Behcet Disease		IIA, B[8]	
	Gastrointestinal involvement of Behcet Disease		III, C[8]	
	Nervous system involvement of Behcet Disease		III, C[8]	
	Joint involvement of Behcet Disease		IB, A[8]	
Cyclophosphamide	Thrombosis manifestations of Behcet Disease	**2nd**	III, C[8]	No HTA Recommendations were issued by the concerned HTA bodies.
	Arterial involvement of Behcet Disease		III, C[8]	

	Pulmonary arterial involvement of Behcet Disease		Strength of recommendation A, Evidence level 4[15]	
Cyclosporine	Ocular manifestations of Behcet Disease	**2nd**	IB/IIA, A/B[8]	No HTA Recommendations were issued by the concerned HTA bodies.
	Acute deep vein thrombosis		III, C[8]	
	Nervous system involvement of Behcet Disease		III, C[8]	
Etanercept	Ocular manifestations of Behcet Disease	**2nd**	Discretionary Recommendation, insufficient-quality evidence[12]	**NICE:** Positive Recommendation[16] **CADTH:** Conditional Positive Recommendation[17] **HAS:** Positive Recommendation[18]
	Joint involvement of Behcet Disease		Not graded[11]	
	Mucocutanous involvement of Behcet Disease		Not graded[11]	
Infliximab	Ocular manifestations of Behcet Disease	**2nd**	Strong recommendation, moderate quality of evidence[12] IA, B[8]	No HTA Recommendations were issued by the concerned HTA bodies.
	Joint manifestations of Behcet Disease		Strong recommendation, good quality of evidence[12]	
	Neuro-Behcet Syndrome		Not graded[11]	
	Gastro-intestinal Behcet Syndrome			
Methotrexate	Ocular manifestations of Behcet Disease	**2nd**	Strong recommendation, moderate quality of evidence[12]	No HTA Recommendations were issued by the

	Gastro-intestinal Behcet Syndrome		Evidence level: 6, Recommendation: A[9]	concerned HTA bodies.
Apremilast	Mucocutanous involvement of Behcet Disease	**2nd**	IB, A[8]	**HAS:** Positive Recommendation[19] **IQWIG:** Negative Recommendation[20]

Table 2. Non-SFDA Registered Drugs Used in the Management of Behcet Disease

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
Triamcinolone Acetonide	Mucocutanous involvement of Behcet Disease	**1st**	IB, A[8] Evidence level: 1b, Grade of recommendation: A[21]
Interferon-alfa	Mucocutanous involvement of Behcet Disease	**2nd**	IB, A[8]
	Ocular manifestations of Behcet Disease		IIA, B[8]
	Joint involvement of Behcet Disease		IB, A[8]

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, there are no available guidelines issued by Saudi bodies for the management of Behcet Disease.

1.2 North American Guidelines

1.2.1 American Academy of Ophthalmology Expert Panel Recommendations for the Use of Anti-Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders (2014)

A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of anti-tumor necrosis factor α (TNF-α) biologic agents in ocular inflammatory conditions[12]. These guidelines cover multiple concitions including Behcet's disease, juvenile arthritis, spondyloarthropathy, sarcoidosis, and others. For the purpose of this report, only recommendations related to BD have been included.

Table 3. Grading the Certainty of Evidence and Strength of Recommendations of the American Academy of Ophthalmology

Recommendations for care are formed based on the body of the evidence. The following body of evidence quality ratings are defined by GRADE	
Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient qualiy	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; any estimate of effect is very uncertain
Key recommendations for care are defined by GRADE as follows	
Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not

Discretionary recommendation	Used when the tradeoffs are less certaindeither because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

The American Academy of Ophthalmology has issued recommendations below[12]:

Ocular Manifestations of Behçet's Disease

- Consideration of anti-TNF therapy with **infliximab** (Strong Recommendation, good-quality evidence) or **adalimumab** (Strong Recommendation, moderate-quality evidence) as first- or second-line corticosteroid-sparing therapy for patients with ophthalmic manifestations of Behçet's disease is recommended.
- Infliximab may be considered as a first- or second-line treatment for acute exacerbations of pre-existing Behçet's disease. Etanercept may be considered for Behçet's patients with uveitis who are intolerant to infliximab and adalimumab (Discretionary Recommendation, insufficient-quality evidence).

1.3 European Guidelines

1.3.1 European League Against Rheumatism (EULAR) Recommendations for the Management of Behçet's Syndrome (2018)

To update the recommendations in the light of these new data under the auspices of the European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs, a task force was formed that included BS experts from different specialties including internal medicine, rheumatology, ophthalmology, dermatology, neurology, gastroenterology, oral health medicine and vascular surgery. The former recommendations were modified, or new recommendations were formed after thorough discussions followed by voting[8].

Table 4. EULAR Certainty of Evidence and Strength of Recommendations

Level of Evidence	
IA	Meta-analysis of RCTs
IB	At least one RCT
IIA	At least one controlled study without randomisation
IIB	At least one type of quasi-experimental study
III	descriptive studies, such as comparative studies, correlation studies or case–control studies
IV	Expert committee reports or opinions and/or clinical experience of respected authorities.

Strength of Recommendation	
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendation from categories I or II evidence
D	Category IV evidence or extrapolated recommendation from categories II or III evidence

The EULAR has issued recommendations below[8]:

Table 5. EULAR Recommendations for the Management of Behçet's Syndrome, with Levels of Evidence, Grade of Recommendations, Voting Rates and Level of Agreement

	Overarching principles and recommendations	Level of evidence	Strength of recommendation
Overarching principles	Behçet's Syndrome (BS) typically exhibits a relapsing and remitting course, with the primary treatment goal being the prompt suppression of inflammatory exacerbations to prevent irreversible organ damage. Optimal care requires a multidisciplinary approach, and treatment should be tailored based on factors such as age, gender, type and severity of organ involvement, and patient preferences. Poor prognosis may be associated with ocular, vascular, neurological, and gastrointestinal involvement, although disease manifestations can ameliorate over time for many patients.	NA	NA

1. Mucocutaneous involvement	**Topical** measures, including **steroids**, are recommended for the treatment of oral and genital ulcers. **Colchicine** is the initial choice for preventing recurrent mucocutaneous lesions, especially when erythema nodosum or genital ulcer predominates. Papulopustular lesions are managed using topical or systemic measures akin to acne vulgaris.	IB/IV	A/D
	Leg ulcers in BS may result from venous stasis or obliterative vasculitis, requiring collaboration with dermatologists and vascular surgeons for comprehensive treatment planning.	IV	D
	Consideration of drugs such as **azathioprine**, **thalidomide**, **interferon-alpha**, **TNF-alpha inhibitors**, or **apremilast** is advised in selected cases.	IB	A
2. Eye involvement	Managing uveitis in BS necessitates collaboration with ophthalmologists, and treatment options include **azathioprine**, **cyclosporine-A**, **interferon-alpha**, or monoclonal **anti-TNF** antibodies. **Systemic glucocorticoids** should be used in conjunction with azathioprine or other immunosuppressives.	IB/IIA	A/B
	High-dose glucocorticoids, **infliximab**, or **interferon-alpha** are recommended for acute sight-threatening uveitis.	IIA	B

	Intravitreal glucocorticoid injection may be considered for unilateral exacerbations alongside systemic treatment.		
3. Isolated anterior uveitis	**Systemic immunosuppressives** could be considered for those with poor prognostic factors such as young age, male sex, and early disease onset.	IV	D
4.Acute deep vein thrombosis	For the management of acute deep vein thrombosis in BS, **glucocorticoids** and **immunosuppressives** such as azathioprine, cyclophosphamide or cyclosporine-A are recommended.	III	C
5. Refractory venous thrombosis	Monoclonal **anti-TNF** antibodies could be considered in refractory patients. **Anticoagulants** may be added, provided the risk of bleeding in general is low and coexistent pulmonary artery aneurysms are ruled out.	III	C
6. Arterial involvement	Pulmonary artery aneurysms management involves recommending **high-dose glucocorticoids** and **cyclophosphamide**. In refractory cases, the consideration of monoclonal anti-TNF antibodies is advisable. In instances where major bleeding risk is present or high, embolization is the preferred approach over open surgery.	III	C
	Aortic and peripheral artery aneurysms require medical treatment with	III	C

	cyclophosphamide and corticosteroids before intervention for repair. Surgery or stenting should not be delayed in symptomatic patients.		
7. Gastrointestinal involvement	Gastrointestinal involvement in BS should be confirmed through endoscopy and/or imaging. Evaluation is crucial to rule out NSAID ulcers, inflammatory bowel disease, and infections like tuberculosis.	III	C
8. Refractory/ severe gastrointestinal involvement	Urgent surgical consultation is essential for cases involving perforation, major bleeding, or obstruction. Glucocorticoids, along with disease-modifying agents like 5-ASA or azathioprine, should be considered during acute exacerbations. Monoclonal anti-TNF antibodies and/or thalidomide may be options for severe and refractory patients.	III	C
9. Nervous system involvement	Acute parenchymal involvement requires treatment with high-dose glucocorticoids followed by gradual tapering, coupled with immunosuppressives like azathioprine. Cyclosporine is to be avoided, and monoclonal anti-TNF antibodies should be considered as a first-line or refractory treatment in severe cases. The initial episode of cerebral venous thrombosis necessitates high-dose glucocorticoids	III	C

	followed by tapering. Short-term addition of anticoagulants may be considered. Screening for vascular disease at extracranial sites is crucial.		
10. Joint involvement	Acute arthritis in BS patients should be initially treated with colchicine. In cases of acute monoarticular disease, intra-articular glucocorticoids can be employed. Recurrent and chronic cases may benefit from consideration of azathioprine, interferon-alpha, or TNF-alpha inhibitors.	IB	A

1.3.2 Position Statement: French Recommendations for the Management of Behçet's Disease (*Orphanet J Rare Dis*, 2021)

The position statement does not provide a specified grade of evidence or level of recommendation.

The French recommendations for the management of BD are summarized below[10]:

- **Systemic corticosteroids** and **immunosuppressive** therapy are imperative for every case of posterior uveitis in Behçet's disease. Severe cases warrant the introduction of corticosteroids and anti-TNFα. Interferon-α is an alternative therapeutic option.
- Unexplained fever or biological inflammation in Behçet's disease necessitates a search for complicated/severe organ involvement, such as cardiac and/or vascular issues.
- Febrile headaches during Behçet's disease may require ruling out cerebral thrombophlebitis through imaging and cerebrospinal fluid examination. Parenchymal neurological involvement often accompanies aseptic meningitis.
- Cerebral thrombophlebitis warrants investigation for intracranial hypertension, which, if persistent and overlooked, may lead to optical atrophy and blindness.
- In cases of parenchymal damage, cerebral lesions are preferentially located in the brainstem, central basal ganglia, and at the capsulo-thalamic level.

- Meningo-rhombencephalitis in Behçet's disease requires careful consideration of infectious causes before attributing it to the disease.
- Vascular involvement in Behçet's disease can be multiple, affecting both venous and arterial vessels, typically large and medium-sized. Superficial venous thromboses often precede deep venous ones.
- Venous thromboses in Behçet's disease, of an inflammatory type, justify systemic anti-inflammatory treatment with corticosteroids and possibly immunosuppressants or immunomodulators (azathioprine, cyclophosphamide, or anti-TNF-α). Anticoagulant use is debated but may be considered in adults during the acute phase and in the absence of bleeding risk, particularly with associated arterial aneurysms.
- Venous thrombosis in children and young adults should prompt a search for other causes of thrombophilia.
- Severe organ damage in Behçet's disease requires specialized care from expert centers, emphasizing the need for a multidisciplinary team.
- Ocular and neurological damage poses the primary risk of sequelae and handicaps in Behçet's disease.
- Severe vascular manifestations, including arterial pulmonary and aortic aneurysms and Budd-Chiari syndrome, are life-threatening.
- **Corticosteroid sparing is a critical goal** due to the cortico-dependent nature and frequent relapses in Behçet's disease.
- Investigation into lack of therapeutic compliance is essential for uncontrolled Behçet's disease.
- **Colchicine** serves as the first-line treatment for mucocutaneous and articular manifestations, with a recommended duration of 3–6 months at a posology of 1–2 mg/day.
- Colchicine posology should be adjusted based on renal and hepatic function, with caution regarding drug interactions and grapefruit consumption.
- Reduction or cessation of immunosuppressant or immunomodulating treatment may be considered, typically after at least 2 years of remission in severe Behçet's disease. Any treatment changes require expert advice.
- Behçet's disease is a chronic condition requiring regular, extended follow-up and therapeutic education.
- Transitioning from pediatric to adult medicine should be established for adolescents affected by Behçet's disease.

1.3.3 British Society for Rheumatology Management of Behcet's Syndrome (2020)

The following guidelines do not provide a specified grade of evidence or level of recommendation.

The British Society for Rheumatology has issued recommendations below[11]:

- The treatment of Behcet's syndrome should be tailored based on clinical features. While skin, mucosa, and joint involvement can impact the quality of life, they typically do not cause permanent damage. However, untreated eye, vascular, nervous system, and gastrointestinal system involvement can lead to serious damage and even be fatal.
- The primary goal of management is to prevent relapses and rapidly suppress inflammation, particularly for major organ involvement that may result in severe damage or fatality. Factors influencing treatment decisions include age, gender, type and severity of organ involvement, disease duration, patient preferences, and organ-specific considerations.

Treatment recommendations for **mucocutaneous involvement** in Behcet's syndrome (BS) include:

- **General measures:**
    - **Maintain oral hygiene:** Recommend maintaining good oral hygiene to all patients, emphasizing the avoidance of irritating behaviors and foods to reduce the occurrence of oral ulcers.
    - **Genital ulcer wound care:** Advise wound care to reduce the risk of secondary bacterial infections for genital ulcers.
- **Colchicine:**
    - Colchicine is considered a pioneering treatment in BS.
    - While its efficacy on oral ulcers and papulopustular lesions is controversial, it has shown effectiveness for genital ulcers and nodular lesions, especially in female patients.
    - Although conflicting results exist, colchicine may be beneficial in some patients, but subpopulations likely to respond are yet to be defined.
- **Local therapeutics:**
    - Local therapeutics such as corticosteroids, NSAIDs, anti-microbials, immunosuppressives, and surface agents may be considered, but more research is needed.
    - Topical pentoxifylline gel is under study for oral ulcers.

- **Combination therapy:**
    - A prospective study combining systemic benzathine penicillin with colchicine showed a decrease in the frequency of genital ulcers, frequency and duration of oral ulcers, and erythema nodosum. This combination may be an alternative for refractory patients.
- **Alternative drugs:**
    - Thalidomide and dapsone can be used for oral and genital ulcers, with caution for thalidomide causing a flare in erythema nodosum.
    - Azathioprine (AZA) is another alternative for mucocutaneous lesions.
    - Apremilast, with promising results from a completed phase III trial, may be a safe novel choice for oral ulcers.
    - Interferon-alpha (IFN-a) and etanercept (TNFi) have shown efficacy for mucocutaneous features.
- **Novel choices:**
    - Interleukin-1 inhibitors (IL-1i) such as anakinra and canakinumab appear effective for mucocutaneous complaints.
    - Interleukin-17 inhibitor (IL-17i) secukinumab and interleukin-12/23 inhibitor (IL-12/23i) ustekinumab may be alternatives for managing mucocutaneous features.
    - Tocilizumab (TCZ), an interleukin-6 inhibitor (IL-6i), may be considered for cases unresponsive to other treatments.

Treatment recommendations for joint involvement in Behcet's syndrome (BS) include:

- **Initial treatment - colchicine:**
    - Colchicine is considered effective and is often used as the initial treatment for acute arthritis in BS, supported by evidence from randomized controlled trials (RCTs).
- **Additional treatments:**
    - **Corticosteroids:** Depot-form and/or low-dose systemic corticosteroids can be effective, serving as additives to colchicine treatment in resistant cases.
    - **Intra-articular glucocorticoids:** Depending on the case, intra-articular glucocorticoids might be considered for monoarticular diseases.

- **NSAIDs:** Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used during acute exacerbations.

- **Disease-modifying drugs:**
  - **Azathioprine (AZA):** RCT data suggests the benefit of AZA in preventing new arthritis attacks in patients with recurrent arthritis.
  - **Interferon-alpha (IFN-a) or etanercept:** Consider IFN-a or etanercept for resistant cases.
  - **Other TNFi (adalimumab and infliximab):** Observational studies suggest efficacy in arthritis, although RCTs are lacking.
  - **Benzathine penicillin:** Consider for controlling joint manifestations in patients with recurrent arthritis attacks despite effective treatment.
- **Chronic course and mimicking spondyloarthropathies:**
  - Some resistant patients with lower extremity oligoarthritis may have a chronic course resembling seronegative spondyloarthropathies.
  - **Conventional DMARDs (csDMARDs):** Drugs such as sulfasalazine, methotrexate, and leflunomide may be considered as possible alternative mono- or combination therapies, especially in refractory cases.
  - **Secukinumab:** Preliminary studies indicate promise in treating articular manifestations in BS.

Treatment recommendations for ocular involvement in Behcet's syndrome (BS) include:

- **High-dose systemic glucocorticoids:**
  - Preferred for acute posterior uveitis attacks due to rapid onset.
  - Not recommended as a sole treatment but can be used as bridging therapy until the effect of other drugs begins.
- **Isolated anterior uveitis:**
  - Patients with isolated anterior uveitis can be treated with topical agents.
- **Systemic immunosuppressive drugs:**
  - Azathioprine (AZA) is recommended, especially in the presence of poor prognostic factors.
  - AZA and ciclosporin-A (CsA) are well-known options with accumulated clinical experience for preserving visual acuity and preventing relapses.

- Methotrexate is a useful alternative option to AZA and CsA.

- **Biologic agents:**
  - Interferon-alpha (IFN-a) and some TNF inhibitors (TNFi) such as infliximab are highly effective options for posterior uveitis.
  - Adalimumab has shown improvement in visual acuity based on case series and reports.
- **Emergency cases:**
  - Acute sight-threatening and severe uveitis in BS is considered an emergency.
  - Pulse methylprednisolone (250–1000 mg for 1–3 days) is recommended.
  - Infliximab or IFN-a can be used as induction therapy.
- **IL-1 inhibitors:**
  - Gevokizumab study for BS uveitis did not show efficacy, but canakinumab and anakinra appear to be useful alternatives needing more trials for confirmation.
- **Other biologic agents:**
  - Golimumab and tocilizumab have been used in BS uveitis, but further studies are needed to establish their efficacy.
- **Intravitreal glucocorticoid injection:**
  - An option for unilateral exacerbations as an adjunct to systemic treatment.
  - Complications are frequent and may include cataracts, increased intraocular pressure, and glaucoma.

Treatment recommendations for Vascular-Behcet's syndrome include:

Venous type:

- **Treatment of acute deep vein thrombosis:**
  - Glucocorticoids and immunosuppressives like AZA and ciclosporin-A are recommended.
  - Cyclophosphamide and TNFi preferred for larger vein thrombosis or recurrent/refractory cases.
- **Budd-Chiari syndrome (BCS):**
  - BS is an important cause of BCS, and diagnosis is crucial.

- Mortality is extremely high if treated only with anticoagulation without immunosuppressive treatment.

- **Use of anticoagulation:**
  - Controversial, and the role of anticoagulation in BS needs clarification.
  - May be considered for refractory cases and larger vein thrombosis.
  - Coexistent pulmonary artery aneurysms should be ruled out before anticoagulation.

Arterial type:

- **Pulmonary artery involvement:**
  - High-dose glucocorticoids and cyclophosphamide recommended.
  - AZA for maintenance therapy in remission, and infliximab in refractory cases.
  - Consider intravascular interventional therapies or open surgery for increased bleeding risk.
- **Aortic and peripheral artery aneurysms:**
  - Similar medical treatment to pulmonary artery involvement.
  - Surgery is required depending on symptoms, type, and size of the aneurysm.
  - Initiate immunosuppressive therapy perioperatively for medical emergencies.

Treatment recommendations for **neuro-Behcet's Syndrome** (NBS) include:

- **Parenchymal involvement:**
  - Treat acute attacks with high-dose glucocorticoids, slow tapering, and immunosuppressives (AZA, TNFi - infliximab).
  - TNFi may be considered in severe or refractory cases, although evidence is not definitive.
  - Avoid cyclosporine (CsA) due to neurological issues.
  - Consider INF-a or tocilizumab for refractory cases.
- **Non-parenchymal involvement:**
  - Treat the first episode of cerebral venous thrombosis with high-dose glucocorticoids followed by tapering.
  - Limited data on adding immunosuppressives to corticosteroids; consider for refractory or relapsing cases.

- Anticoagulants may be added for a short duration, with careful exclusion of arterial aneurysms.

Treatment recommendations for **gastrointestinal involvement** (entero-Behcet's syndrome) include:

- Use glucocorticoids during acute exacerbations with disease-modifying agents (sulfasalazine, AZA).
- TNFi (infliximab) and/or thalidomide recommended for refractory cases.
- Multidisciplinary approach for severe cases (perforation, major bleeding, obstruction).

Treatment recommendations for **miscellaneous features** include:

- **Amyloidosis:**
  - Uncommon but highly morbid complication causing end-stage renal failure.
  - Predictors for development are unknown.
  - Tocilizumab or INF-a may be effective in treating symptoms and findings related to amyloidosis.

Table 6. Drugs (Dose, Indication, Side Effects…) That Are Useful in Managing Behcet's Syndrome

Drugs	Route of administration	Recommended dose range	Indications	Possible side effects and precautions
Corticosteroids	Topical (0.1% triamcinolone acetonide)	TID	Oral ulcers	
	Systemic	Depot 40 mg methylpred-nisolone acetate	Erythema nodosum	Fatigue, weight gain, abdominal pain, hypertrichosis, other possible steroid side effects (cataract, osteoporosis etc.)
	Systemic (PO or IV)	Low to high dose AND / OR Pulse corticosteroids	Oral ulcers, genital ulcers, erythema nodo-sum, arthritis, vascular,	

			neurological, gastrointestinal	
	Intravitreal (for uveitis) and intra-articular (for arthritis) corticosteroids may be used for selected cases depending on clinicians experience and indications.			
Dapsone	PO	100 mg daily	Oral, genital ulcers	Diarrhea, nausea / vomiting, headache, hemolysis, methemo-globinemia, cholestatic hepatitis
Thalidomide	PO	100-300 mg/day	Oral ulcers, genital ulcers, arthritis, gastrointestinal	Increase in erythema nodosum, skin rash, dizziness, sedation, fatigue, thrombo-embolism, peripheral neuropathy, teratogenicity (phocomelia)
Apremilast	PO	30 mg BID	Oral ulcers	Diarrhea, nausea / vomiting, headache
Pentoxifylline	5% gel (topical)	QID	Oral ulcers[a]	-
Benzathine Penicillin	IM	1.2 million units/3 weeks	Oral ulcers[a], genital ulcers[a], arthritis[a]	Allergy
Colchicine	PO	1-2 mg/day	Oral ulcers (?), genital ulcers, erythema nodosum, arthritis	Diarrhea, hepatotoxicity, cytopenia, myopathy
AZA	PO	2 mg/kg/day	Oral ulcers, genital ulcers, arthritis, uveitis, gastrointestinal, uveitis	Nausea / vomiting, skin rash, cytopenia, drug interaction with allopurinol
Cyclosporine-A	PO	5 mg/kg/day	Uveitis	Occuring NBS, hypertension, kidney failure, cosmetic side effects

Sulfasalazine	PO	2-4 g/day	Gastrointestinal	Headache, nausea, vomiting, abdominal pain, rash, itching, azoospermia
IFN-a	SC	6 million units, 3/week (3–9 million units)	Oral ulcers, genital ulcers, erythema nodosum, Papulopustular, uveitis, NBS[a], vascular[a], gastrointestinal[a]	Elevated transaminases, cytopenia, thyroid dysfunction, flu- like symptoms
Infliximab (TNFi)	IV	5 mg/kg 0–2–6 weeks Continue with every 6–8 weeks	Arthritis, uveitis, NBS, vascular, gastrointestinal	Injection side effects (for SC), infections, Viral hepatitis and TBC reactivation Precautions for cancer
Adalimumab (TNFi)	SC	40 mg / 2 weeks	Uveitis, NBS[a], vascular[a], gastrointestinal[a]	
Etanercept (TNFi)	SC	50 mg/week	Oral ulcers (?), genital ulcers, erythema nodosum, papulopustular	
Tocilizumab (IL-6i)	IV	8 mg/kg/4 weeks	Uveitis, NBS[a], amyloidosis[a]	Infections, viral hepatitis and TBC reactivation Elevated lipid parameters and transaminases
Secukinumab (IL-17i)	SC	150–300 mg/4 weeks	Oral ulcers[a], arthritis[a]	Injection side effects (for s.c.), infections, Precautions for inflammatory bowel disease
Ustekinumab (IL12/23i)	SC	45–90 mg	Oral ulcers[a]	

		0–4–12 weeks Continue with every 12 weeks		
Anakinra (IL-1i)	SC	100 mg daily	Oral ulcers[a], genital ulcers[a], uveitis[a]	Injection side effects (for s.c.), infections
Canakinumab (IL-1i)	SC	150 mg / 6 weeks	Oral ulcers[a], genital ulcers[a], uveitis[a]	

[a]These drugs need to be experienced more and have more clinical studies for recommendation in these indications. They may be considered for selected refractory cases de- pending on clinicians' experiences

B.I.D: bis in die (two times each day); NBS: Neuro-Behcet's syndrome; Q.I.D: quater in die (four times each day); Ref.: References; T.I.D: ter in die (three times each day); TBC: tuberculosis

1.4 International Guidelines

1.4.1 Japanese Society of Gastroenterology Evidence-Based Diagnosis and Clinical Practice Guidelines for Intestinal Behcet's Disease (2020)

These guidelines by the Japanese Society of Gastroenterology were established to provide appropriate evidence for decision making by both patients and health-care providers for the management of intestinal BD[9].

Table 7. Grading the Certainty of Evidence and Strength of Recommendations of the Japanese Society of Gastroenterology

Level of recommendation		Contrast to evidence level
A	Strong recommendation to perform	Mainly 1
B	Recommendation to perform	Mainly 2, 3
C1	Consideration to perform with insufficient evidence	Mainly 4, 5, 6
C2	Inadvisability due to no evidence	No evidence
D	Recommendation not to perform	Invalid or harmful evidence

The Japanese Society of Gastroenterology has issued recommendations below[9]:

- Consider the use of the following treatments for intestinal BD:

        - 5-ASA drugs and salazosulfapyridine (SASP) for mild to moderate cases.
        - Corticosteroids, TNF inhibitors, and nutrition therapy for moderate to severe cases.
        - Induction treatment by surgery for intractable cases.
        - Recommend considering the use of these treatments (Evidence level: 5, Recommendation: A).
    - For remission maintenance therapies in intestinal BD, consider:
        - 5-ASA drugs.
        - Thiopurine drugs.
        - TNF inhibitors.
        - Nutrition therapy.
        - Recommend considering these therapies (Evidence level: 5, Recommendation: A).
    - Suggest the administration of 5-ASA drugs for inducing and maintaining remission in intestinal BD (Evidence level: 5, Recommendation: A).
    - Recommend the use of corticosteroids for intestinal BD with moderate activity or higher, or for cases not responding well to other induction therapies (Evidence level: 4, Recommendation: B).
    - Consider treatment with thiopurines for patients dependent and refractory to steroids, and for those in whom TNF inhibitors against intestinal BD are ineffective (Evidence level: 4, Recommendation, C1).
    - Propose treatment with thiopurines to prevent the recurrence of intestinal BD in patients who have previously undergone partial intestinal resection (Evidence level: 3, Recommendation: C1).
    - It is proposed that methotrexate should not be solely administered for intestinal BD (Evidence level: 6, Recommendation: A).
    - In genetically predisposed populations, consider gene screening of polymorphism in NUDT15 R139C before the use of AZA or 6-mercaptopurine to prevent severe thiopurine-induced complications (Evidence level: 3, Recommendation: A).
    - Do not recommend the administration of AZA or 6-mercaptopurine to patients with NUDT15 R139C homozygous (T/T) polymorphism (Evidence level: 3, Recommendation: N/A).
    - Consider enteral nutrition (EN) as an additional treatment for intestinal BD that is refractory to drug treatment (Evidence level: 5, Recommendation: B).

- The efficacy of total parenteral nutrition (TPN) for the treatment of intestinal BD is not clear. Recommend its use only in those with severe disease activity and for a limited period (Evidence level: 6, Recommendation: B).
- The efficacy of colchicine for the treatment of intestinal BD is not clear. Recommend avoiding the administration of colchicine alone as medical treatment for mucosal inflammation and ulcers (Evidence level: 6, Recommendation: B).
- Recommend treatment with TNF inhibitors for patients with complete and incomplete types of intestinal BD unresponsive to conventional treatments. The use of a TNF inhibitor is recommended in such intractable cases (Evidence level: 2b, Recommendation: A).
- Propose treatment with tacrolimus for patients with intestinal BD unresponsive to conventional treatments, based on cases in which tacrolimus was effective (Evidence level: 5, Recommendation, C1).
- Perform surgical treatment in patients with intestinal perforation, severe stricture, large abscess, and massive gastrointestinal bleedings, which are absolute indications (Evidence level: 4, Recommendation: A).
- Propose surgical treatment in patients who are refractory to medications and have low quality of life because of intestinal complications such as fistula, which are relative indications (Evidence level: 4, Recommendation: A).
- Although pediatric-onset intestinal BD patients should be treated as in adult patients with BD, recommend minimizing the use of corticosteroids to avoid growth disturbance (Evidence level: 6, Recommendation: A).

1.4.2 Japanese Dermatological Association Guidelines for the Treatment of Skin and Mucosal Lesions in Behcet's Disease: A Secondary Publication (2020)

These guidelines by the Japanese Dermatological Association discuss the current standard diagnosis and treatment protocol for the mucocutaneous lesions of BD in Japan. Detailed strategies for the management of this disease should be individualized by physicians based on the features in any particular patient[21].

Table 8. Grading the Certainty of Evidence and Strength of Recommendations of the Japanese Dermatological Association

Strength of recommendation classifications	
A	Strongly recommended for use (there is at least one instance of L1 evidence or high-quality L2 evidence showing its effectiveness).

A*	Recommended for use (there is evidence of effectiveness corresponding to A, but its strength of recommendation is inferior when taking into account adverse events).
B	Recommended for use (there is at least one instance of low-quality L2 evidence, high-quality L3 evidence or extremely high-quality L4 evidence showing its effectiveness).
C1	Recommended as an alternative (there is low-quality L3–4 evidence, multiple instances of high-quality L5 evidence or L6 evidence approved by the committee).
C2	Not recommended due to insufficient evidence (at present).
D	Discouraged for use (there is high-quality evidence that it is ineffective or harmful).
Evidence level classifications	
1	Systematic reviews, meta-analyses.
2	One or more RCT.
3	Non-RCT (including before-and-after trials with statistical analyses).
4	Analytical–epidemiological studies (cohort studies and case–control studies).
5	Descriptive studies (case reports and case-series studies).
6	The opinions of expert committee members and individual experts.

The Japanese Dermatological Association has issued recommendations below[21]:

Oral Aphthous Ulcers in Behcet's Disease:

- **Topical steroids** are effective and strongly recommended for treating oral aphthous ulcers in Behcet's disease (Evidence level: 1b, Grade of recommendation: A).
- **Systemic steroids** are proposed as a treatment option for oral aphthous ulcers in Behcet's disease (Evidence level: 5, Grade of recommendation: C1).
- **Systemic colchicine** is recommended if there are no lesions in major organs (Evidence level: 2, Grade of recommendation: B).
- Rebamipide and sucralfate are recommended options for treatment (Evidence level: 2, Grade of recommendation: B).
- Use of antimicrobial agents is proposed for oral ulcers in the absence of lesions in major organs. For those with major organ involvement, combination with colchicine is suggested (Evidence level: 3, Grade of recommendation: C1).

- TNF-a inhibitors are likely to be effective and are proposed as an option after careful consideration of the indications in selected patients (Evidence level: 1b, Grade of recommendation: C1).
- Apremilast for oral aphthous ulcers is likely to be effective, and its administration is recommended (Evidence level: 1b, Grade of recommendation: B).

Genital Ulcers in Behcet's Disease:

- Topical steroids are proposed for treating genital ulcers (Evidence level: 6, Grade of recommendation: C1).
- Systemic steroids are proposed as a treatment option for intractable genital ulcers (Evidence level: 6, Grade of recommendation: C1).
- Oral colchicine is effective and recommended (Evidence level: 1b, Grade of recommendation: B).
- TNF-a inhibitors are proposed as an option for intractable genital ulcers resistant to standard treatment after careful consideration of the indications for these agents (Evidence level: 5, Grade of recommendation: C1).

Erythema Nodosum in Behcet's Disease:

- Topical steroids are proposed for treating erythema nodosum (Evidence level: 6, Grade of recommendation: C1).
- NSAIDs are proposed for the treatment of erythema nodosum (Evidence level: 4, Grade of recommendation: C1).
- Minocycline is proposed for erythema nodosum (Evidence level: 4, Grade of recommendation: C1).
- Dapsone is proposed for erythema nodosum (Evidence level: 1b, Grade of recommendation: C1).
- Colchicine is recommended for erythema nodosum (Evidence level: 1b, Grade of recommendation: B).
- Systemic steroids are recommended for erythema nodosum (Evidence level: 1b, Grade of recommendation: B).
- TNF-a inhibitors are proposed for severe erythema nodosum (Evidence level: 1b, Grade of recommendation: C1).

Acneiform Eruptions in Behcet's Disease:

- Topical steroids are proposed for managing acneiform eruptions (Evidence level: 6, Grade of recommendation: C1).

- Oral antimicrobial agents are proposed for treating acneiform eruptions (Evidence level: 5, Grade of recommendation: C1).
- Oral colchicine is recommended for acneiform eruptions (Evidence level: 2, Grade of recommendation: B).

Superficial Thrombophlebitis in Behcet's Disease:

- Systemic steroids and an immunosuppressant such as cyclosporin are proposed as an option for superficial thrombophlebitis (Evidence level: 4, Grade of recommendation: B-C1).
- Warfarin is likely to be effective, and adding warfarin to treatment with a steroid or an immunosuppressant is proposed (Evidence level: 5, Grade of recommendation: C1).
- The use of colchicine for the treatment of superficial thrombophlebitis is proposed (Evidence level: 5, Grade of recommendation: B-C1).

1.4.3 Japanese National Research Committee for Behçet's Disease Recommendations for the Management of the Vascular Involvement in Behçet's Disease – Secondary Publication (2023)

Guidelines issued by the Japanese National Research Committee for Behcet's disease follow the grading system detailed in table 7 above. The main recommendations are summarized below[15].

- Initiation of corticosteroids is recommended as the primary treatment for acute DVT with inflammation. In serious or refractory cases, the concurrent use of immunosuppressants like AZA should be considered (Strength of recommendation C1, Evidence level 3).
- Anticoagulants should be considered as a treatment option for deep vein thrombosis, except in patients at high risk of bleeding (Strength of recommendation C1, Evidence level 5).
- For nonpulmonary aneurysms due to BD-related inflammatory vascular lesions, the strongly recommended approach involves corticosteroids along with immunosuppressants such as cyclophosphamide and azathioprine (Strength of recommendation A, Evidence level 4).
- Corticosteroids, coupled with immunosuppressants like cyclophosphamide, are recommended for pulmonary arterial involvement (Strength of recommendation B, Evidence level 3).
- Consideration of TNF inhibitors is advisable for cases of serious vascular involvement, especially in situations refractory to conventional

immunosuppressive therapy (Strength of recommendation C1, Evidence level 3).

- Severe aortic regurgitation warrants prosthetic valve replacement in accordance with Japanese guidelines on valvular heart disease management. Aortic root replacement is recommended for patients with aortic root involvement. Graft replacement is advised for thoracic and abdominal aortic aneurysms with a high risk of rupture, determined by size, enlargement speed, and shape (Strength of recommendation C1, Evidence level 4).
- Absolute operative indications, including rupture, impending rupture, and rapidly enlarging aneurysm, call for aneurysm resection, graft insertion, or ligation of afferent and efferent vessels (Strength of recommendation C1, Evidence level 4).
- Endovascular treatment, such as stent graft insertion, is considered a viable option for aneurysms (Strength of recommendation C1, Evidence level 4).
- Surgical procedures should be avoided during the active inflammatory phase and scheduled electively after inflammation subsides. In urgent surgeries, initiation of corticosteroids and immunosuppressants is recommended prior to the procedure (Strength of recommendation B, Evidence level 3).

1.4.4 Recommendations for the Management of Neuro-Behçet's Disease by the Japanese National Research Committee for Behçet's Disease (2020)

These guidelines by the Japanese National Research Committee for Behçet's Disease were established to provide appropriate evidence for decision making by both patients and health-care providers for the management of Neuro-Behçet's Disease[22].

Table 9. Grading the Certainty of Evidence and Strength of Recommendations of the Japanese National Research Committee for Behçet's Disease

Evidence level	
1a	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs)
1b	At least one RCT
2a	Cohort studies with simultaneous controls
2b	Cohort studies with past controls

3	Case-control studies (retrospective)
4	Studies without before and after comparison or comparison with controls
5	Single case reports or reports of case series
6	Experts' opinions or reports of expert committee
Recommendation level	
A	Strongly recommended
B	Recommended
C1	Maybe considered, but no evidence
C2	Not recommended due to the lack of evidence
D	Recommended not to do

The Japanese National Research Committee for Behçet's Disease has issued recommendations below [22]:

- Include all cases meeting diagnostic criteria* for ANB and CPNB in the "moderate or severe" CNS manifestations category (Strength of recommendation A, Level of evidence 3).
- If prednisolone at a dose ≥20 mg/day (oral or intravenous) is ineffective, consider high-dose therapy, including steroid pulse therapy (Strength of recommendation B, Level of evidence 3).
- If corticosteroids at a moderate or higher dose are insufficient, consider concurrent use of infliximab (Strength of recommendation C1, Level of evidence 5).
- Initiate colchicine (1.0-2.0 mg/day) immediately after the first attack and continue for 5 years (Strength of recommendation B, Level of evidence 3).
- Discontinue cyclosporine; for ocular involvement, consider using infliximab (Strength of recommendation A, Level of evidence 3).
- As these drugs are considered less effective for preventing relapse than colchicine, active use of these drugs is not recommended (Strength of recommendation C1, Level of evidence 3).
- If an attack relapses, even after colchicine use, consider treatment with infliximab (Strength of recommendation C1, Level of evidence 5).
- Conduct a thorough evaluation of neurological findings, along with brain MRI and CSF IL-6, after improvement or reduction of corticosteroids (Strength of recommendation B, Level of evidence 3).
- Symptoms of ANB do not necessarily precede CPNB (Strength of

recommendation A, Level of evidence 3).

- Ensure CSF IL-6 decreases below 17 pg/mL as soon as possible (Strength of recommendation B, Level of evidence 3).
- Initiate infliximab immediately if there is no improvement in neurological manifestations and CSF IL-6 does not decrease below 17 pg/mL with maximal MTX doses (Strength of recommendation B, Level of evidence 2b).
- Goals should include controlling CSF IL-6 at a low level, preventing symptom progression, and avoiding brainstem atrophy progression on MRI (Strength of recommendation B, Level of evidence 2b).
- Perform necessary examinations until the therapeutic regimen is established; thereafter, conduct brain MRI at least annually and CSF IL-6 examination once a year or more frequently if possible (Strength of recommendation B, Level of evidence 3).

1.5 Systematic Reviews and Meta Analyses

The table below tackles systematic reviews and meta-analyses issued in **2018** and **2022** for Behcet Disease.

Table 10. Systematic Review and Meta-Analysis for the Management of Behcet Disease

Author (year)	Study Title	Primary Objective	Outcomes	Results
Zhang et al. (2022)[23]	"The efficacy and safety of anti-tumor necrosis factor agents in the treatment of intestinal Behcet's disease, a systematic review and meta-analysis"	To evaluate the effectiveness (proportion of clinical or endoscopic remission) and safety (incidence of ADRs) of anti-TNF agents in the treatment of intestinal Behcet's disease.	**Primary outcome:** Evaluate the clinical efficacy through measures of clinical remission and endoscopic remission/mucosal healing **Secondary Outcomes:** Evaluate additional information on other efficacy measures as well as safety by monitoring adverse events	• 13 studies were included involving a total of 739 patients with intestinal Behcet's disease. All studies were single-arm cohort studies. • The pooled proportion of patients achieving clinical remission at 3, 6, 12 and 24 months after anti-TNF treatment was 61%, 51%, 57% and 38% respectively. • The pooled proportion achieving endoscopic remission/mucosal healing at the same timepoints was 66%, 82%, 65% and 69%. • Subgroup analyses found similar effectiveness for infliximab and adalimumab specifically. • Other efficacy outcomes such as marked clinical improvement, corticosteroid discontinuation and CRP recovery also indicated appreciable effectiveness of anti-TNF agents. • The pooled proportion of overall adverse drug reactions for infliximab was 22%. Pooled proportions for infusion reactions and infections were 12% and 21%. • The majority of reported adverse reactions involved infusion reactions or infections, with

				severe reactions being rare. No deaths were reported. • **In summary, the results suggest anti-TNF agents, particularly infliximab and adalimumab, are an effective therapy for intestinal Behcet's disease with an acceptable safety profile. They may be a promising treatment option for patients not adequately responding to conventional therapies.**
Ozguler et al. (2018)[24]	"Management of major organ involvement of Behcet's syndrome: a systematic review for update of the EULAR recommendations"	To assess the efficacy and safety of treatment modalities for major organ involvement of Behcet's syndrome (BS), to inform the update of the EULAR recommendations for the management of BS	**Primary outcome:** Evaluate efficacy, effectiveness measures that were specific to each treatment comparison or condition **Secondary outcome:** Evaluate safety, time-course, relapse/recurrence rates and other disease outcomes.	• There were only 9 randomized controlled trials included in the review. Most studies assessing treatment for major organ involvement in Behcet's syndrome were observational studies. • Observational studies with IFN-alpha and TNF inhibitors like infliximab showed beneficial results for refractory uveitis. • A meta-analysis of case-control studies found that immunosuppressives significantly decreased the recurrence rate of deep vein thrombosis, while anticoagulants did not. • CYC and high dose glucocorticoids decreased mortality in pulmonary arterial aneurysms and postoperative complications in peripheral artery aneurysms. • Beneficial results for gastrointestinal involvement were seen with 5-ASA derivatives and AZA as first line, and with thalidomide and TNF inhibitors for refractory cases.

				• Observational studies found improved outcomes with immunosuppressives and glucocorticoids for nervous system involvement. • A meta-analysis showed an increased risk of developing nervous system involvement with cyclosporine-A. • Biologics, mostly TNF inhibitors, started gaining importance in treating refractory major organ involvement in Behcet's syndrome. • **In summary, the review found limited RCT evidence but observational studies generally supported the use of TNF inhibitors and IFN-alpha for refractory involvement, while conventional agents like immunosuppressives and corticosteroids remained first-line options.**

Section 2.0 Drug Therapy

2.1 Immunosuppressive Agents

2.1.1 Adalimumab

Information on Adalimumab is detailed in the table below[25–27]:

Table 11. Adalimumab Drug Information

SCIENTIFIC NAME ADALIMUMAB	
SFDA Classification	Prescription
SFDA	Off-label
US FDA	Off-label
EMEA	Off-label
MHRA	Off-label
PMDA	Yes
Indication (ICD-10)	M35.2
Drug Class	Immunosuppressant Agent
Drug Sub-class	Tumor Necrosis Factor (TNF) Blocking Agent
ATC Code	L04AB04
Pharmacological Class (ASHP)	Antirheumatics - Disease Modifying Anti-rheumatic Drugs (DMARDs)
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	Initial: SUBQ: 80 mg as a single dose. Maintenance: SUBQ: 40 mg every other week beginning 1 week after initial dose
Maximum Daily Dose Adults*	Maximum dose not established
Dose (pediatrics)	**Children ≥2 years and Adolescents:** 10 kg to <15 kg: SUBQ: 10 mg every other week. 15 to <30 kg: SUBQ: 20 mg every other week. ≥30 kg: SUBQ: 40 mg every other week.

Maximum Daily Dose Pediatrics*	Maximum dose not established
Adjustment	Kidney impairment: No dosage adjustment necessary for any degree of kidney dysfunction Hepatic impairment: no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	TNFs should be used in combination with an oral disease-modifying antirheumatic drug (DMARD) such as azathioprine to help prevent development of potentially neutralizing antibodies.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Adalimumab needs to be prescribed by a consultant rheumatologist, ophthalmologist for Behcet Disease depending on the symptoms the patients present with.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Adalimumab is used as second-line or later treatment, particularly in cases where conventional therapies like corticosteroids or immunosuppressive agents are insufficient or not well-tolerated; mainly considered for corticosteroid-sparing treatment.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: Injection-site reactions, upper respiratory infections, headache **Most serious**: infections, malignancies, hepatitis B reactivation

Drug Interactions*	**<u>Category X:</u>** • Abatacept • Abrocitinib • Anakinra • Anifrolumab • Baricitinib • BCG products • Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) • Brivudine • Canakinumab • Certolizumab • Chikungunya Vaccine (Live) • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucrvacitinib • Etrasimod • Filgotinib • Mumps- Rubella- or Varicella-Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Rilonacept • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Vaccines (Live) • Vedolizumab • Yellow Fever Vaccine
Special Population	○ Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs (DMARDs) prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing

	cycle (eg, for medications administered every 4 weeks, schedule surgery 5 weeks from last administered dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications. ○ Surgery patients: Limited experience with patients undergoing surgical procedures while on therapy; consider long half-life with planned procedures. Monitor closely for infection
Pregnancy	Use of immune modulating therapies in pregnancy should be individualized to optimize maternal disease and pregnancy outcomes. The American Academy of Dermatology considers TNFα blocking agents for the treatment of psoriasis to be compatible with pregnancy. When treatment for inflammatory bowel disease is needed in pregnant women, appropriate biologic therapy can be continued without interruption. Serum levels should be evaluated prior to conception and optimized to avoid subtherapeutic concentrations or high levels which may increase placental transfer. Dosing can be adjusted so delivery occurs at the lowest serum concentration. For

	adalimumab, the final injection can be given 2 to 3 weeks prior to the estimated date of delivery (1 to 2 weeks if weekly dosing), then continued 48 hours postpartum.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha blocking agents are considered compatible with breastfeeding.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. *Canadian labeling:* Known hypersensitivity to adalimumab or any component of the formulation; severe infection (eg, sepsis, tuberculosis, opportunistic infection); moderate-to-severe heart failure (NYHA class III/IV)
Monitoring Requirements	CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy including risk factors (chest X-ray if TB positive); Hepatitis C virus/hepatitis B virus (HBV) screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening in high risk patients (baseline) (AAD-NPF [Menter 2019]); signs/symptoms of infection, hypersensitivity reaction, new autoimmune disorder (including lupus-like syndrome), or malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Monitor

	improvement of symptoms and physical function assessments.
Precautions	*Concerns related to adverse effects:* o Antibody formation: Formation of neutralizing anti-drug antibodies may occur with biologic tumor necrosis factor (TNF) inhibitors and may be associated with loss of efficacy. o Hematologic disorders: Rare cases of pancytopenia and aplastic anemia have been reported with TNF-blockers. Patients must be advised to seek medical attention if they develop signs and symptoms suggestive of blood dyscrasias; discontinue if significant hematologic abnormalities are confirmed. Use with caution in patients with a history of significant hematologic abnormalities. *Disease-related concerns:* o Active infection: Do not initiate therapy in patients with an active infection, including clinically important localized infection. o HIV: Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided they have normal CD4 counts, no viral load, and no recent opportunistic infections. o Immunizations: Patients should be brought up to date with all immunizations before initiating therapy; live vaccines should not be given concurrently. There are no data available concerning the

	effects of therapy on vaccination or secondary transmission of live vaccines in patients receiving therapy.
Black Box Warning	**Malignancy:** Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with tumor necrosis factor (TNF)–blockers, including adalimumab. **Infections:** Patients treated with adalimumab are at increased risk of developing serious infections that may lead to hospitalization or death. Reported infections include the following: Active tuberculosis (TB), including reactivation of latent TB, Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, Bacterial, viral, and other infections caused by opportunistic pathogens, including Legionella and Listeria.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Adalimumab.**

Table 12. Adalimumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Adalimumab	NICE[13]	**Conditional Positive Recommendation** – 26 July 2017 Adalimumab is recommended as a cost-effective option for treating non-infectious uveitis in the posterior segment of the eye in adults, if there is:

		• active disease and • an inadequate response or intolerance to immunosuppressants and • systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and • worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema). The committee concluded that the ICER for unilateral disease with a risk of blindness was likely to be in the range normally considered cost effective, and recommended dexamethasone for treating active non-infectious uveitis with worsening vision and a risk of blindness.
	CADTH	Not applicable
	HAS[14]	**Positive Recommendation** – January 3, 2020 Favorable opinion for reimbursement within the same restricted scope of reimbursable indications as the other presentations of HUMIRA. Important in the management of adult uveitis.
	IQWIG	Not applicable
	PBAC	Not applicable

CONCLUSION STATEMENT- Adalimumab

Adalimumab is a biologic medication that works as a tumor necrosis factor-alpha (TNF-α) inhibitor. It is used in various autoimmune conditions, including Behçet's disease, which is a chronic, multisystemic inflammatory disorder. It is used especially in cases where conventional treatments, such as corticosteroids or immunosuppressive agents, are inadequate or associated with significant side effects. It is usually given as 80 mg SQ as a single dose for initial dosing and for maintenance 40 mg SQ every other week beginning 1 week after initial dose. Its use for Behcet Disease is backed up by NICE[13] with a conditional positive recommendation and HAS[14] with a positive recommendation supporting its benefit from an economic standpoint. Limitations for the use of Adalimumab include malignancy and infections.

2.1.2 Azathioprine

Information on Azathioprine is detailed in the table below[28]:

Table 13. Azathioprine Drug Information

SCIENTIFIC NAME AZATHIOPRINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off-label use for Behcet Disease
EMEA	Off label (approved for Non-infectious uveitis)
MHRA	Off label
PMDA	Off label
Indication (ICD-10)	M35.2
Drug Class	Immunosuppressant Agent
Drug Sub-class	N/A
ATC Code	L04AX01
Pharmacological Class (ASHP)	Immunosuppressant Agent
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Initial: 50 mg PO once daily; increase by 50 mg every 4 weeks as tolerated, to goal maintenance dose of 2.5 mg/kg once daily; may be given in combination with a glucocorticoid
Maximum Daily Dose Adults*	Maximum dose not established
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Kidney impairment: CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose. Cl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. Hemodialysis: dialyzable, administer 50-100% of the dose. Administer after hemodialysis if need to administer on

	dialysis day. If not, provide a 50% supplemental dose. Peritoneal dialysis: Initial: Administer 50% to 100% of the dose. CRRT and sustained, low efficiency diafiltration with PIRRT: Administer 75% to 100% of the dose. Hepatic impairment: no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, CU, QL, MD
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Azathioprine is generally given in combination with a glucocorticoid.
G (Gender Edit): N/A	N/A
MD (Physician Specialty Edit):	Azathioprine can be prescribed by a consultant rheumatologist, ophthalmologist, dermatologist for Behcet Disease depending on the symptoms the patients present with.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	Some experts suggest not exceeding 200mg/day.
ST (Step Therapy):	Azathioprine is generally considered a second-line treatment option for Behcet Disease, meaning it is often used when first-line treatments are insufficient or not well-tolerated
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: Nausea, vomiting, leukopenia, infection **Most serious**: GI effects, Hematologic toxicity, Infections, Liver dysfunction, Malignancy, Pancreatitis
Drug Interactions*	**Category X:** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine

	• Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine [INT] • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Febuxostat • Fexinidazole • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mercaptopurine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)

Special Population	Consider testing for thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (nucleotide diphosphatase; NUDT15) deficiency in patients who develop severe bone marrow toxicities (may require dose reduction or discontinuation). Dosage reduction or selection of alternative therapy is recommended in patients with TPMT and/or NUDT15 deficiency.
Pregnancy	Azathioprine crosses the placenta. Available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy
Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant. Monitoring infant blood cell count 10 to 15 days after breastfeeding is initiated or in infants with frequent infections.
Contraindications	Hypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis, patients with rheumatoid arthritis and a history of treatment with alkylating agents (e.g., cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk

	of malignancy with azathioprine treatment
Monitoring Requirements	Obtain CBC with differential and platelets, total bilirubin, liver function tests, and creatinine clearance. Consider testing for thiopurine S-methyltransferase (TPMT) deficiency particularly in patients with abnormally low CBC unresponsive to dose reduction. Assess for signs of photosensitivity reactions. Consider timing and types of vaccines. Assess for signs/symptoms of infection and malignancy (e.g., splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Dosage adjustment may be needed if patient is taking allopurinol.
Precautions	Use with caution in patients with hepatic or renal impairment. Mercaptopurine: Azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression and should be avoided. Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be enhanced (depending on the azathioprine dose). Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis.
Black Box Warning	Malignancy: include post-transplant lymphoma and hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Azathioprine.**

Table 14. Azathioprine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Azathioprine	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Azathioprine

Azathioprine is often considered a second-line treatment option for Behçet's syndrome. It may be used when first-line treatments, such as corticosteroids and colchicine, are insufficient to control symptoms or if long-term immunosuppression is needed. It is usually given as 50 mg PO once daily and the dose is increased by 50 mg every 4 weeks as tolerated, to achieve a maintenance dose of 2.5 mg/kg once daily. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Limitations for the use of Azathioprine include malignancy.

2.1.3 Cyclophosphamide

Information on Cyclophosphamide is detailed in the table below [29,30]:

Table 15. Cyclophosphamide Drug Information

SCIENTIFIC NAME CYCLOPHOSPHAMIDE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off-label
EMA	Off-label
MHRA	Off-label

PMDA	Off-label
Indication (ICD-10)	M35.2
Drug Class	Antineoplastic, Alkylating Agent, Antirheumatic, Immunosuppressant
Drug Sub-class	Nitrogen Mustard
ATC Code	L01AA01
Pharmacological Class (ASHP)	Antineoplastic Agent
DRUG INFORMATION	
Dosage Form	Film-coated tablet, Powder for solution for injection
Route of Administration	IV use, Oral use
Dose (Adult) [DDD]*	Orally (1–3 mg/kg/day) or by intravenous pulse (500–1,000 mg/m2 every month for 6–9 months)
Maximum Daily Dose Adults*	Maximum dose has not been established; some experts do not exceed 1,000 mg/dose IV. Do not exceed 150 mg/day oral.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	CrCl 10 to 29 mL/minute: Administer 75% or 100% of PO normal dose. CrCl <10 mL/minute: Administer 50%, 75%, or 100% of PO normal dose. IV: Shorter, low-dose regimen (500 mg IV once every 2 weeks for 6 doses): No dosage adjustment necessary. IV: Longer, high-dose regimen (500 to 1,000 mg/m2 IV pulses): CrCl <30 mL/ minute: Reduce initial dose to 500 mg/m2 Hemodialysis, intermittent (thrice weekly): Moderately dialyzable (20% to 50% removal based on limited data with low-flux dialyzers): Administer 50% or 75% of the normal dose. On dialysis

	days, administer after hemodialysis, allowing at least 12 hours before the next hemodialysis session. Peritoneal dialysis: Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange. CRRT: Administer 100% of the normal dose Hepatic adjustment: no dosage adjustments provided in the manufacturer's labeling. Floyd 2006 has recommended: Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. Serum bilirubin >5 mg/dL: Avoid use.
Prescribing edits*	CU, MD, QL, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Used in combination with corticosteroids for the management of Behcet disease with acute deep vein thrombosis and arterial involvement.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy should prescribe Cyclophosphamide.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	For IV: Some experts recommend not exceeding 1,000 mg/dose. For Oral: 150mg/day.
ST (Step Therapy):	Cyclophosphamide is considered a second-line or third-line therapy for Behcet's disease, reserved for cases that are severe, refractory, or involve life-threatening manifestations.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A

SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** leukopenia, neutropenia, anemia, arrythmias and pericarditis. **Most serious:** Bone marrow suppression and infection, Cardiotoxicity, Hemorrhagic cystitis, Hepatotoxicity, Pulmonary toxicity, Second primary malignancy
Drug Interactions*	**Category X:** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine Depends on International labeling • Baricitinib • BCG (Intravesical) (Immunization) • Brivudine [INT] • Cholera Vaccine Depends on International labeling • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) Depends on International labeling • Etanercept • Fexinidazole • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) Depends on International labeling • Japanese Encephalitis Virus Vaccine (Live/Attenuated) Depends on International labeling • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine

	• Mumps Virus Vaccine Depends on International labeling • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) Depends on International labeling • Poliovirus Vaccine (Live/Trivalent/Oral) • Rotavirus Vaccine Depends on International labeling • Ruxolitinib (Topical) • Smallpox Vaccine Live Depends on International labeling • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Voclosporin • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated) Depends on International labeling.
Special Population	Dosing adjustment for toxicity: Infants, Children, and Adolescents: Hematologic toxicity: May require dose reduction or treatment interruption. Hemorrhagic cystitis, severe: Discontinue treatment. Older Adult Considerations Toxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and elevated WBC, may not occur. Lethargy and confusion may be more prominent signs of infection; adjust dose for renal function.

Pregnancy	Cyclophosphamide crosses the placenta and can be detected in amniotic fluid. In patients with life- or organ-threatening maternal disease, cyclophosphamide may be used in the second or third trimesters only when an alternative therapy is not available
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Cyclophosphamide is not recommended for use in breastfeeding mothers with autoimmune and systemic inflammatory diseases. breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last cyclophosphamide dose. Others recommend breastfeeding be avoided for at least 6 weeks after the last dose of cyclophosphamide
Contraindications	History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation; urinary outflow obstruction. Canadian labeling: Additional contraindications (not in the US labeling): Severe myelosuppression, severe renal or hepatic impairment, active infection (especially varicella zoster), severe immunosuppression.
Monitoring Requirements	Obtain CBC with differential and platelets, serum electrolytes, BUN, serum creatinine, and urinalysis. Dosage in the obese should be weight based. Premedicate with an antiemetic and MESNA. Assess for signs and symptoms of hemorrhagic cystitis, renal toxicity, pulmonary toxicity, cardiac toxicity, and liver toxicity.

Precautions	Use with caution in patients with hepatic or renal impairment. Hypersensitivity: Possible cross-sensitivity with other alkylating agents may occur. Some cyclophosphamide injection dosage forms may contain alcohol. The alcohol content (in some dosage forms) may affect the CNS and impair the ability to drive or operate machinery.
Black Box Warning	**N/A**
REMS*	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Cyclophosphamide.**

Table 16. Cyclophosphamide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cyclophosphamide	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Cyclophosphamide

Cyclophosphamide is generally considered in Behcet's disease when there is severe and refractory involvement, especially when other treatments have not been successful in controlling the disease. It is often reserved for more advanced cases or when there are life-threatening manifestations such as acute deep vein thrombosis and arterial involvement. It is usually given as 1–3 mg/kg/day orally or by intravenous pulse 500–1,000 mg/m2 every month for 6–9 months. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Limitations for the use of Azathioprine include malignancy. Limitations for the use of Cyclophosphamide include bone marrow suppression, cardiotoxicity, and hepatotoxicity.

2.1.4 Cyclosporine

Information on Cyclosporine are detailed in the table below[31]:

Table 17. Cyclosporine Drug Information

SCIENTIFIC NAME CYCLOSPORINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off label
EMEA	Off label
MHRA	Off label
PMDA	Off label
Indication (ICD-10)	M35.2
Drug Class	Immunosuppressant Agent
Drug Sub-class	Calcineurin Inhibitor
ATC Code	L04AD01
Pharmacological Class (ASHP)	Immunosuppressant Agent
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion, capsule, oral solution
Route of Administration	Oral Use
Dose (Adult) [DDD]*	Uveitis (off-label use): Oral: 2.5 to 5 mg/kg/day in 2 divided doses; gradually decrease to maintenance dose; used alone or in conjunction with other corticosteroids. An expert panel recommends initial dose of 3 to 5 mg/kg/day; reducing dose, once inflammation was under control, to 2 to 3 mg/kg/day until a maintenance dose of 1 mg/kg/day is achieved
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Severe hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling; however,

	metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction. Kidney impairment prior to treatment initiation: no adjustment necessary. During treatment: Nontransplant indications: If serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine. For patients receiving renal replacement: Consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if benefits outweigh risks of further kidney injury
Prescribing edits*	ST, QL, MD
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Only physicians experienced in immunosuppressive therapy should prescribe Cyclosporine such as

	rheumatologists, ophthalmologists (for ocular involvement of Behcet Disease).
PA (Prior Authorization):	N/A
QL (Quantity Limit):	Experts suggest not exceeding 5 mg/kg daily.
ST (Step Therapy):	Cyclosporine is considered in cases of Behçet's disease where there is significant organ involvement, such as ocular or vascular manifestations. It may be used as a second-line therapy in patients who do not respond well to or cannot tolerate other treatments.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypertension, Hirsutism, Urinary tract infection, Tremor **Most serious:** • Diabetes mellitus • Drug-induced gingival overgrowth • Drug-induced thrombotic microangiopathy • Hepatotoxicity • Hyperkalemia • Hypertension • Infections • Malignancy • Nephrotoxicity • Neurotoxicity
Drug Interactions*	**Category X:** • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Aliskiren • AMILoride • Asunaprevir • Atorvastatin Depends on International labeling

	• Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Bilastine Depends on Renal Function • Bosentan • Brivudine [INT] • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Disulfiram Depends on Dosage Form • DOXOrubicin Conventional • Dronedarone • Ebola Zaire Vaccine (Live) • Elagolix • Elagolix, Estradiol, and Norethindrone • Elbasvir and Grazoprevir • Eplerenone • Erdafitinib • Fexinidazole • Filgotinib • Foscarnet • Fusidic Acid (Systemic) • Grapefruit Juice Depends on Route • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Lasmiditan • Lercanidipine • Lovastatin • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Methotrimeprazine Depends on Dosage Form • Mifamurtide

	• MiFEPRIStone Depends on Indication • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Ornidazole Depends on Dosage Form and International labeling • Pacritinib • PAZOPanib • Pimecrolimus • Pimozide • Pitavastatin • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Red Yeast Rice • Revefenacin • Rotavirus Vaccine • Ruxolitinib (Topical) • Secnidazole Depends on Dosage Form • Simeprevir • Simvastatin • Sirolimus (Protein Bound) • Smallpox Vaccine Live • Sparsentan • XSpironolactone • Tacrolimus (Systemic) • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Tertomotide • Tofacitinib • Topotecan Depends on Route • Treosulfan • Triamterene • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • VinCRIStine (Liposomal)

	• Voxilaprevir • Yellow Fever Vaccine • Zavegepant • Zoster Vaccine (Live/Attenuated)
Special Population	Older Adult Considerations Cyclosporine may be used in combination therapy for the treatment of severe rheumatoid arthritis. Monitor renal function closely during therapy and decrease dose as needed.
Pregnancy	Cyclosporine crosses the placenta. Cyclosporine can be used during pregnancy for refractory cases of lupus nephritis and other rheumatic and musculoskeletal diseases in patients who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended.
Lactation	Cyclosporine is present in breast milk. Due to the potential for serious adverse in the breastfeeding infant, the manufacturer recommends a decision be made to discontinue cyclosporine or to discontinue breastfeeding, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to cyclosporine or any component of the formulation. IV cyclosporine is contraindicated in hypersensitivity to polyoxyethylated castor oil. Additional contraindications (not in the US labeling): Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer).

Monitoring Requirements	Obtain plasma concentrations, renal function tests, liver function tests, and serum glucose. Monitor blood pressure periodically and with addition, modification, or deletion of other medications. Assessing for hypersensitivity reactions with IV use. Assess for signs and symptoms of liver toxicity, secondary malignancy, diabetes, and infection. Assess for progressive cognitive or motor deficits. Consider MRI if posterior reversible encephalopathy syndrome is suspected. Assess other medications patient is taking; alternative therapy or dosage adjustment may be needed. When transferring patients with previously poor absorption of cyclosporine (non-modified), monitor trough levels at least twice weekly. For myasthenia gravis patients, abrupt cessation of cyclosporine may cause rapid deterioration of myasthenic symptoms and myasthenic crisis.
Precautions	Product may contain corn oil or ethanol or polyoxyethylated castor oil or propylene glycol. Discontinuation of therapy: Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis. Vaccines: Live, attenuated vaccines may be less effective; vaccination should be avoided.
Black Box Warning	• Only health care providers experienced in the management of systemic immunosuppressive therapy

	for the indicated disease should prescribe cyclosporine. • Immunosuppression • Erratic absorption and bioavailability • Psoriasis patients previously treated with psoralens plus ultraviolet A (PUVA) and, to a lesser extent, methotrexate or other immunosuppressive agents, ultraviolet B (UVB), coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking cyclosporine. • Hypertension/nephrotoxicity
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Cyclosporine.**

Table 18. Cyclosporine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cyclosporine	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Cyclosporine

Cyclosporine is considered as a second-line treatment for Behçet's disease, especially when there is significant organ involvement, such as ocular manifestations (posterior uveitis). It is usually given as 5 mg/kg/day and may be used together with glucocorticoids and azathioprine as an alternative to infliximab. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities.

Limitations for the use of Cyclosporine include nephrotoxicity, hypertension, and psoriasis.

2.1.5 Etanercept

Information on Etanercept is detailed in the table below[27,32,33]:

Table 19. Etanercept Drug Information

SCIENTIFIC NAME ETANERCEPT	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off-label
EMEA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	M35.2
Drug Class	Immunosuppressant Agent
Drug Sub-class	Tumor Necrosis Factor (TNF) Blocking Agent
ATC Code	L04AB04
Pharmacological Class (ASHP)	Antirheumatics - Disease Modifying Anti-rheumatic Drugs (DMARDs)
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	50 mg/week SQ
Maximum Daily Dose Adults*	Maximum dose not established
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Kidney impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied) Hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied)

Prescribing edits*	CU, MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	TNFs should be used in combination with an oral disease-modifying antirheumatic drug (DMARD) such as azathioprine to help prevent development of potentially neutralizing antibodies.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Adalimumab needs to be prescribed by a consultant rheumatologist, ophthalmologist for Behcet Disease depending on the symptoms the patients present with.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Etanercept may be considered for Behçet's patients with uveitis who are intolerant to infliximab and adalimumab.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: Injection site reactions (redness, itching, pain), Upper respiratory infections, Headache, Dizziness, Rash **Most serious**: infections, malignancies
Drug Interactions*	**Category X:** • Abatacept • Abrocitinib • Anakinra • Anifrolumab • Baricitinib • BCG products • Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) • Brivudine • Canakinumab

	• Certolizumab • Chikungunya Vaccine (Live) • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucrvacitinib • Etrasimod • Filgotinib • Mumps- Rubella- or Varicella-Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Rilonacept • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Vaccines (Live) • Vedolizumab • Yellow Fever Vaccine
Special Population	○ Older adult: Infection has been reported at a higher incidence; use caution in elderly patients. ○ Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs (DMARDs) prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing cycle (eg, for medications administered every 4 weeks, schedule surgery 5 weeks from last administered

	dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications. o Pediatric: Malignancies have been reported among children and adolescents. o Varicella virus exposure: Patients with a significant exposure to varicella virus should temporarily discontinue therapy; treatment with varicella zoster immune globulin should be considered.
Pregnancy	Etanercept crosses the placenta. Use of immune modulating therapies in pregnancy should be individualized to optimize maternal disease and pregnancy outcomes.
Lactation	According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα) blocking agents are considered compatible with breastfeeding.
Contraindications	Sepsis

	Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to etanercept or any component of the formulation; patients at risk of sepsis syndrome (eg, immunocompromised, HIV positive).
Monitoring Requirements	CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy (chest X-ray if TB positive); hepatitis B virus (HBV)/hepatitis C virus screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening (baseline); signs/symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, or malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Monitor improvement of symptoms and physical function assessments.
Precautions	**Anaphylaxis/hypersensitivity reactions:** o Immediate discontinuation and appropriate therapy initiation are recommended if an anaphylactic or serious allergic reaction occurs. **Antibody formation:** o Formation of neutralizing anti-drug antibodies may occur with TNF inhibitors, potentially leading to a loss of efficacy. **Autoimmune disorder:** o Positive antinuclear antibody titers have been detected, and rare cases of autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis, have been reported.

	Monitoring is advised, and treatment should be discontinued if symptoms develop. **Demyelinating CNS disease:** o Rare cases of new-onset or exacerbation of CNS demyelinating disorders have occurred, and caution is advised, especially in patients with preexisting or recent-onset CNS demyelinating disorders. **Heart failure:** o Worsening and new-onset heart failure have been reported, and caution is recommended, particularly in patients with heart failure or decreased left ventricular function. **Hematologic disorders:** o Rare cases of pancytopenia and aplastic anemia have been reported, and patients should seek medical attention for signs of blood dyscrasias. Discontinuation is advised if significant hematologic abnormalities are confirmed. **Hepatitis B:** o Rare reactivation of hepatitis B has occurred, necessitating evaluation for HBV prior to initiation. Monitoring during and after treatment in HBV carriers is crucial, with consideration for interruption of therapy if reactivation occurs. **Infections:** o Patients receiving etanercept are at an increased risk of serious infections, and monitoring for

	signs/symptoms of infection during and after treatment is essential. Discontinuation is recommended for serious infection or sepsis. **Malignancy:** o Lymphoma and other malignancies (some fatal) have been reported in children, adolescents, and adults receiving TNF-blocking agents, including etanercept. Periodic skin examinations are advised, especially for those at an increased risk of skin cancer. **Tuberculosis:** o TB disease, including reactivation of latent TB, has been reported. Evaluation for TB risk factors and infection, along with monitoring and treatment, is recommended during therapy. **Alcoholic hepatitis:** o Use with caution in patients with moderate to severe alcoholic hepatitis. Compared to placebo, the mortality rate in patients treated with etanercept was similar at 1 month but significantly higher after 6 months. **Granulomatosis with polyangiitis:** o Use is not recommended in patients with granulomatosis with polyangiitis who are receiving immunosuppressive therapy due to higher incidence of noncutaneous solid malignancies. **HIV**:

	○ Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided they have normal CD4 counts, no viral load, and no recent opportunistic infections. **Seizure disorders:** ○ Use with caution in patients with a history of seizures; new-onset or exacerbation of seizures have been reported. **Immunizations:** ○ Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.
Black Box Warning	**Malignancy:** Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with tumor necrosis factor (TNF)–blockers, including adalimumab. **Infections:** Patients treated with adalimumab are at increased risk of developing serious infections that may lead to hospitalization or death. Reported infections include the following: Active tuberculosis (TB), including reactivation of latent TB, Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, Bacterial, viral, and other infections caused by opportunistic pathogens, including Legionella and Listeria.

REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Etanercept.**

Table 20. Etanercept HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Etanercept	NICE[16]	**December 16, 2015: Positive Recommendation** Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorizations, as options for treating polyarticular juvenile idiopathic arthritis (JIA), including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is: for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, methotrexate
	CADTH[17]	**July 2017** **Conditional positive recommendation:** The CADTH Canadian Drug Expert Committee (CDEC) recommends that Erelzi (etanercept biosimilar) be reimbursed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS), if the following criterion and conditions are met: **Criterion:** For use in patients for whom etanercept is considered to be the most appropriate treatment option. **Conditions:** - Reimburse in a manner similar to Enbrel. - The cost of treatment with Erelzi should provide significant cost savings for jurisdictions

		compared with the cost of treatment with existing etanercept products.
	HAS[18]	**January 16, 2014: Positive Recommendation** The actual benefit of ENBREL remains significant in the MA indications: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis in adults
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Etanercept

Etanercept is a biologic medication that works as a tumor necrosis factor-alpha (TNF-α) inhibitor. It is used in various autoimmune conditions, including Behçet's disease, which is a chronic, multisystemic inflammatory disorder. It is used especially in cases where conventional treatments, such as corticosteroids or immunosuppressive agents, are inadequate or associated with significant side effects. It is usually given as 50 mg/week. Its use for Behcet Disease is backed up by NICE[16] and HAS[18] with positive recommendations and CADTH[17] with a conditional positive recommendation supporting its benefit from an economic standpoint. Limitations for the use of Etanercept include malignancy and infections.

2.1.6 Infliximab

Information on Infliximab are detailed in the table below[27,34]:

Table 21. Infliximab Drug Information

SCIENTIFIC NAME INFLIXIMAB	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off label
EMEA	Off label
MHRA	Off label
PMDA	Yes
Indication (ICD-10)	M35.2
Drug Class	Immunosuppressant Agent
Drug Sub-class	Tumor Necrosis Factor (TNF) Blocking Agent

ATC Code	L04AD01
Pharmacological Class (ASHP)	Antirheumatics - Disease Modifying Anti-rheumatic Drugs (DMARDs)
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	Initially 5 mg/kg at 0–2–6 weeks. Continue with every 6–8 weeks
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Kidney Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment** **Initial or dose titration with preexisting liver cirrhosis:** No dosage adjustment necessary for any degree of liver dysfunction. **Elevated liver-associated enzymes during treatment:** ***Infliximab-induced hepatoxicity:*** **Note:** Idiosyncratic elevation of hepatic transaminases occur in >30% of patients at around 10 weeks; especially in those with elevated ALT at baseline or MASLD. **AST/ALT <5 times ULN:** Continue infliximab therapy with frequent (eg, every 2 weeks) LFT monitoring; most cases (~75%) resolve without further intervention. **AST/ALT ≥5 times ULN:** Discontinue infliximab therapy and consult hepatologist. May be indicative of infliximab-induced autoimmune hepatitis, which may cause severe liver

	injury and can be fatal or lead to liver transplantation.
Prescribing edits*	CU, MD
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	TNFs should be used in combination with an oral disease-modifying antirheumatic drug (DMARD) such as azathioprine to help prevent development of potentially neutralizing antibodies.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Infliximab needs to be prescribed by a consultant rheumatologist, ophthalmologist for Behcet Disease depending on the symptoms the patients present with.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Injection-site reactions, upper respiratory infections, headache, and abdominal pain **Most serious**: infections, malignancies, hepatitis B reactivation and neurological disorders
Drug Interactions*	**Category X:** • Abatacept • Abrocitinib • Anakinra • Anifrolumab • Baricitinib • BCG products • Biologic Disease-Modifying Antirheumatic Drugs (DMARDs) • Brivudine • Canakinumab

	• Certolizumab • Chikungunya Vaccine (Live) • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucrvacitinib • Etrasimod • Filgotinib • Mumps- Rubella- or Varicella-Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Rilonacept • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Vaccines (Live) • Vedolizumab • Yellow Fever Vaccine
Special Population	Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs prior to surgery and plan surgery after the next dose is due. Surgery can occur after holding medication for 1 full dosing cycle (eg, for medications administered every 4 weeks, schedule surgery 5 weeks from last administered dose); therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples

	are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). Decisions to withhold therapy should be based on shared decision making; ensure the patient and their provider weigh risks of interrupting therapy and disease control versus risks of continuing therapy and surgical complications.
Pregnancy	Infliximab crosses the placenta. Based on available data, an increased risk of major birth defects has not been observed following infliximab exposure during pregnancy. Information related to this class of medications is emerging, but based on available data, tumor necrosis factor alpha (TNFα)-blocking agents are considered to have low to moderate risk when used in pregnancy. Use of immune-modulating therapies in pregnancy should be individualized to optimize maternal disease and pregnancy outcomes
Lactation	Infliximab is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα)-blocking agents, including infliximab, are considered compatible with breastfeeding.
Contraindications	Previous severe hypersensitivity (eg, anaphylaxis, hypotension, serum sickness) to infliximab, murine proteins, or any component of the formulation; doses >5 mg/kg in patients with moderate or severe heart failure (NYHA class III/IV).

	Canadian labeling: Additional contraindications (not in US labeling): Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections); use in patients with moderate or severe heart failure (NYHA class III/IV).
Monitoring Requirements	CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy (chest Xray if TB positive); hepatitis b virus (HBV)/hepatitis C virus screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening (baseline); LFTs (baseline and periodically during therapy; more frequently in patients with elevated LFTs; discontinue if >5 times ULN); signs/symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss); signs and symptoms suggestive of blood dyscrasias (eg, persistent fevers). During infusion, if reaction is noted, monitor vital signs every 2 to 10 minutes, depending on reaction severity, until normal. If a serious reaction occurs (eg, cardiovascular or cerebrovascular reaction), discontinue the infusion. Monitor improvement of symptoms and physical function assessments.
Precautions	○ **Antibody formation:** Formation of neutralizing anti-drug antibodies may occur with biologic tumor necrosis factor

	(TNF) inhibitors and may be associated with loss of efficacy. ○ **Cardiovascular/cerebrovascular reactions during and following infusion:** Cerebrovascular accidents, MI (some fatal), hypotension, hypertension, and arrhythmias have been reported within 24 hours of infusion. Transient vision loss has also been reported during or within 2 hours of infusion. Discontinue therapy if serious reaction occurs. ○ **Hematologic disorders:** Hematologic toxicities (eg, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported (may be fatal). ○ **Active infection:** Do not initiate infliximab therapy in patients with an active infection, including clinically important localized infection. ○ **HIV:** Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided they have normal CD4 counts, no viral load, and no recent opportunistic infections. ○ **Seizure disorders:** Use with caution in patients with a history of seizures; discontinue if significant CNS adverse reactions develop. ○ **Solid organ transplant:** Consider holding infliximab prior to living donor solid organ transplant (eg, hold IV infliximab for at least 4

	weeks; hold SUBQ infliximab for 1 week).
Black Box Warning	**Malignancy:** Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with tumor necrosis factor (TNF)–blockers, including adalimumab. **Infections:** Patients treated with adalimumab are at increased risk of developing serious infections that may lead to hospitalization or death. Reported infections include the following: Active tuberculosis (TB), including reactivation of latent TB, Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, Bacterial, viral, and other infections caused by opportunistic pathogens, including Legionella and Listeria.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Infliximab.**

Table 22. Infliximab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Infliximab	NICE	Not applicable
	CADTH	Not applicable
	HAS	Not applicable
	IQWIG	Not applicable
	PBAC	Not applicable

CONCLUSION STATEMENT- Infliximab

Infliximab is a biologic medication that works as a tumor necrosis factor-alpha (TNF-α) inhibitor. It is used in various autoimmune conditions, including Behçet's disease, which is a chronic, multisystemic inflammatory disorder. It is used especially in cases where conventional treatments, such as corticosteroids, are inadequate or associated with significant side effects. It is usually given as 5 mg/kg at 0–2–6 weeks and there is a need to continue with it every 6–8 weeks. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Limitations for the use of Infliximab include malignancy and infections.

2.1.7 Methotrexate

Information on Methotrexate is detailed in the table below[35]:

Table 23. Methotrexate Drug Information

SCIENTIFIC NAME METHOTREXATE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off label
EMEA	Off label
MHRA	Off label
PMDA	Off label
Indication (ICD-10)	M35.2
Drug Class	Antineoplastic Agent; Antirheumatic, Disease Modifying; Immunosuppressant Agent
Drug Sub-class	Antimetabolite (Antifolate)
ATC Code	L01BA01
Pharmacological Class (ASHP)	Antineoplastic Agent
DRUG INFORMATION	
Dosage Form	Solution for injection, Solution for injection in pre-filled syringe, oral solution, tablet
Route of Administration	IV Injection, IM Injection, Oral use
Dose (Adult) [DDD]*	**Oral, SUBQ, IM:** Initial: 7.5 to 15 mg once weekly (in combination with folic acid). Increase dose by 2.5 to 5

	mg/week every 4 to 12 weeks if needed based on response (maximum: 25 mg/week); current guidelines suggest titrating to a target dose of ≥15 mg/week within 4 to 6 weeks of initiation. Once disease remission is achieved, may gradually reduce dose (eg, by 2.5 mg/week every 1 to 2 months) to 15 mg/week to limit adverse effects. No DDD established since highly individualized use and wide dosage ranges.
Maximum Daily Dose Adults*	Maximum: 20 to 25 mg/week
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Hepatic impairment prior to treatment: There are no dosage adjustments provided in the manufacturer's labeling; use with caution. The following adjustments have been recommended: Bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. Bilirubin >5 mg/dL: Avoid use. Hepatotoxicity during treatment: Withhold, consider a reduced dose, or discontinue methotrexate as appropriate. Altered Kidney Function: here are no dosage adjustments provided in the manufacturer's labeling. General dosage adjustment recommendations: Kintzel 1995: • CrCl >60 mL/minute: No dose adjustment necessary. • CrCl 46 to 60 mL/minute: Administer 65% of normal dose. • CrCl 31 to 45 mL/minute: Administer 50% of normal dose. • CrCl <30 mL/minute: Avoid use.

	Aronoff 2007: • CrCl >50 mL/minute: No dose adjustment necessary. • CrCl 10 to 50 mL/minute: Administer 50% of dose. • CrCl <10 mL/minute: Avoid use. Avoid use in hemodialysis and peritoneal dialysis. Administer 50% of dose in CRRT.
Prescribing edits*	CU, MD, QL, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	Methotrexate is to be given in combination with folic acid.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Methotrexate can be prescribed by a specialized rheumatologist for Behcet Disease.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	Maximum: 20 to 25 mg/week
ST (Step Therapy):	Methotrexate is considered as a second-line or adjunctive therapy, especially for mucocutaneous and joint involvement of Behcet Disease that may not respond adequately to first-line treatments like colchicine.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: diarrhea, nausea, hepatotoxicity, fatigue, headache, cough **Most serious**: Dermatologic toxicity, GI toxicity, Hematologic toxicity, Hepatotoxicity, Infection, Nephrotoxicity, Neurotoxicity, Pulmonary toxicity
Drug Interactions*	**Category X:** • Abrocitinib

	• Acitretin • Aminolevulinic Acid (Systemic) • BCG (Intravesical) Depends on Dose • BCG (Intravesical) • BCG Vaccine (Immunization) Depends on Dose • Brivudine [INT] • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dichlorphenamide • Dipyrone • Fexinidazole • Filgotinib Depends on Dose • Foscarnet • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Nitrous Oxide • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Tertomotide • Typhoid Vaccine • Varicella Virus Vaccine • Yellow Fever Vaccine
Special Population	Toxicity to methotrexate or any immunosuppressive is increased in the elderly. Must monitor carefully. For rheumatoid arthritis and psoriasis, immunosuppressive therapy should only be used when disease is active and

	less toxic, traditional therapy is ineffective. Recommended doses should be reduced when initiating therapy in the elderly due to possible decreased metabolism, reduced renal function, and presence of interacting diseases and drugs. Adjust dose as needed for renal function (CrCl).
Pregnancy	Methotrexate crosses the placenta. Following exposure during the first trimester, methotrexate may increase the risk of spontaneous abortion, skull anomalies, facial dysmorphism, CNS, limb and cardiac abnormalities; intellectual impairment may also occur. Intrauterine growth restriction and functional abnormalities may occur following second or third trimester exposure. Consider the benefits and risks of methotrexate and risks to the fetus when prescribing methotrexate to a pregnant patient with a neoplastic disease. The use of methotrexate for the treatment of non-neoplastic indications is contraindicated in pregnancy.
Lactation	Methotrexate and 7-hydroxymethotrexate are present in breast milk. According to the manufacturer, breastfeeding should be discontinued during treatment and for 1 week after the final methotrexate dose. If an infant is exposed to lower doses of methotrexate (maternal doses <0.4 mg/kg/week) via breast milk, consider monitoring the infant CBC at 1 and 3 months of age.
Contraindications	History of severe hypersensitivity (including anaphylaxis) to methotrexate or any component of the formulation; breastfeeding. Additional contraindications for patients with

	psoriasis, rheumatoid arthritis or polyarticular-course juvenile idiopathic arthritis: Pregnancy, alcoholism, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes (overt or laboratory evidence); preexisting blood dyscrasias (eg, bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia). Canadian labeling: Additional contraindications (not in the US labeling): Severe renal impairment (including end-stage renal disease with or without dialysis); females of childbearing potential (until pregnancy is excluded); concomitant use with nitrous oxide anesthesia
Monitoring Requirements	Obtain CBC with differential and platelets, serum creatinine, BUN, liver function tests (bilirubin, alkaline phosphatase, and transaminase), pulmonary function tests (if drug-induced lung disease suspected), and chest x-ray. Obtain methotrexate levels and urine pH with high doses. Dosage in the obese should be based on the actual body weight. Assess other medicines patient is taking; alternate therapy or dosage adjustment may be needed. Assess closely for toxicity in patients with ascites, pleural effusion, decreased folate stores, liver impairment, or renal impairment.
Precautions	• Do not administer nonsteroidal anti-inflammatory drugs (NSAIDs) prior to or during high dose methotrexate therapy; may increase and prolong serum methotrexate levels.

	• Concomitant use of proton pump inhibitors with methotrexate (primarily high-dose methotrexate) may elevate and prolong serum methotrexate levels and metabolite (hydroxymethotrexate) levels. May lead to toxicities; use with caution. • Immunization with live vaccines is not recommended; cases of disseminated vaccinia infections due to live vaccines have been reported. • Vitamins containing folate may decrease response to systemic methotrexate (in patients with neoplastic diseases); folate deficiency may increase methotrexate toxicity. Folic acid supplementation may be indicated in patients receiving methotrexate for non-neoplastic conditions. • Fatal errors have occurred when methotrexate was administered as a daily dose instead of a weekly dose. Verify the indication before administration • Intrathecal safety: When used for intrathecal administration, intrathecal medications should not be prepared during the preparation of any other agents. • Methotrexate overexposure: Glucarpidase may be used for methotrexate overexposure; it is approved for the treatment of toxic plasma methotrexate concentrations (>1 micromole/L) in patients with delayed clearance due to renal impairment. Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol

	(≥99 mg/kg/day) have been associated with a potentially fatal toxicity.
Black Box Warning	Oral: • Serious adverse reactions of the bone marrow, GI tract, liver, lungs, skin, and kidneys. Withhold or discontinue methotrexate tablets as appropriate. • Hypersensitivity: contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis. • Embryo-fetal toxicity: contraindicated in pregnancy. Methotrexate Injection: • Intrathecal and high-dose therapy: use preservative-free formulation. Formulations with benzyl alcohol can cause severe central nervous toxicity or metabolic acidosis. Use only preservative-free methotrexate injection for treatment of neonates or low-birth-weight infants and for intrathecal use. Do not use benzyl alcohol–containing formulations for high-dose regimens unless immediate treatment is required, and preservative-free formulations are not available. • Hypersensitivity: contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis • Appropriate use: adverse reactions of the bone marrow, GI tract, liver, lungs, skin, and kidneys. • Pregnancy: embryo-fetal toxicity. Not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Verify the

	pregnancy status of females of reproductive potential prior to initiating therapy. Advise females and males of reproductive potential to use effective contraception during and after treatment with methotrexate. • Bone marrow suppression: and aplastic anemia with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs). • Renal impairment: require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration • Hepatotoxicity: generally only after prolonged use • Pneumonitis: may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible. may require interruption of treatment and careful investigation. • GI toxicity: reported with concomitant administration of methotrexate (usually in high dosage) along with some NSAIDs. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise hemorrhagic enteritis and death from intestinal perforation may occur. • Secondary malignancy: may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress,

	appropriate treatment should be instituted. • Dermatologic toxicity: Recovery has been reported with discontinuation of therapy. • Opportunistic infections: especially Pneumocystis jirovecii pneumonia • Other serious reactions: Closely monitor for infections and adverse reactions of the bone marrow, kidneys, liver, nervous system, GI tract, lungs, and skin. Withhold or discontinue methotrexate injection as appropriate. • Radiotherapy: Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis. Experienced physician (injection): Methotrexate should be used only by health care providers whose knowledge and experience include the use of antimetabolite therapy.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methotrexate.**

Table 24. Methotrexate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methotrexate	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Methotrexate

Methotrexate is known for its anti-inflammatory and immunosuppressive effects. It is not typically considered a first-line treatment for Behçet's disease but may be used in cases where other treatments, such as colchicine or corticosteroids, are insufficient to control symptoms or when there is organ involvement. It is usually given as 7.5 to 15 mg once weekly orally/SQ/IM (in combination with folic acid). Folic acid at a dose of 5-10mg/week is suggested to reduce MTX side effects. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Limitations for the use of Methotrexate include bone marrow suppression, hepatotoxicity, and pneumonitis.

2.2 Antigout agents

2.2.1 Colchicine

Information on Colchicine is detailed in the table below[36]:

Table 25. Colchicine Drug Information

SCIENTIFIC NAME COLCHICINE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Off label
EMEA	Off label
MHRA	Off label
PMDA	Off label
Indication (ICD-10)	M35.2
Drug Class	Anti-gout agents
Drug Sub-class	Tubulin inhibitors
ATC Code	M04AC01
Pharmacological Class (ASHP)	Antigout Agents
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	1 to 2 mg/day PO (or 1.2 to 1.8 mg/day) in 2 to 3 divided doses
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A

Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Kidney impairment:** No specific dose adjustments recommended; consider risks/benefits of utilizing the usual indication-specific dose versus a reduced dose. **Hepatic Impairment:** Concurrent use of colchicine and P-gp or strong CYP3A4 inhibitors is contraindicated in hepatic impairment. Fatal toxicity has been reported. Treatment of gout flare with colchicine is not recommended in patients with hepatic impairment receiving prophylactic colchicine.
Prescribing edits*	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common**: diarrhea, nausea, myalgia, and peripheral neuropathy **Most serious**: myelosuppression, rhabdomyolysis, multi-organ failure, respiratory failure, and cardiac toxicity (arrhythmias and myocardial damage).
Drug Interactions*	• Antihepaciviral Combination Products • Fexinidazole • Fusidic acid • Grapefruit juice • Lasmiditan • Nirmatrelvir and ritonavir

	• Pacritinib • Sparsenten • Taurursodiol
Special Population	Use with caution in older adults; consider dosage adjustments.
Pregnancy	Colchicine can be continued during pregnancy in females with rheumatic and musculoskeletal diseases. Available guidelines recommend continuing colchicine during pregnancy for the treatment of conditions such as FMF when there are no acceptable alternatives and discontinuation of treatment may lead to uncontrolled disease and adverse pregnancy outcomes. Increased monitoring during pregnancy is recommended; amniocentesis is not warranted.
Lactation	Colchicine is considered compatible with breastfeeding and use should be continued in women with familial Mediterranean fever. Avoiding breastfeeding 2 to 4 hours after the maternal dose may decrease exposure to the breastfed infant.
Contraindications	Concomitant use of a P-glycoprotein (P-gp) inhibitor or strong CYP3A4 inhibitor in presence of renal or hepatic impairment. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. *Canadian labeling:* Additional contraindications (not in US labeling): Hypersensitivity to colchicine; serious GI, hepatic, renal, and cardiac disease; existing blood dyscrasias.
Monitoring Requirements	CBC; renal and hepatic function tests; signs/symptoms of colchicine toxicity

	(early signs include nausea, vomiting, diarrhea, and abdominal pain), particularly in patients with increased risk of accumulation (renal or hepatic impairment, concomitant use of P-gp inhibitors or CYP3A4 inhibitors, chronic therapy).
Precautions	○ **Blood dyscrasias:** Can cause myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia, which can be life-threatening or fatal. ○ **Neuromuscular toxicity:** Can cause neuromuscular toxicity and rhabdomyolysis. If a patient develops signs of neuromuscular toxicity, discontinue therapy, investigate other causes, and treat appropriately. ○ **Fatal overdose:** Accidental and intentional fatal overdoses have been reported. Dosage associated with fatal toxicity is variable (e.g., wide dosage range).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Colchicine.**

Table 26. Colchicine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Colchicine	NICE	N/A
	CADTH	N/A

	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Colchicine

Colchicine is used in the management of Behçet's disease, a condition characterized by recurrent oral and genital ulcers, skin lesions, and inflammation in various parts of the body. The use of colchicine in Behçet's disease is part of the broader treatment approach aimed at controlling inflammation and managing symptoms. It is usually the first line agent and is given as 1 to 2 mg/day PO (or 1.2 to 1.8 mg/day) in 2 to 3 divided doses. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Limitations for the use of Colchicine include myelosuppression, rhabdomyolysis, multi-organ failure, respiratory failure, and cardiac toxicity (arrhythmias and myocardial damage).

2.3 Immunomodulating Agents

2.3.1 Apremilast

Information on Apremilast is detailed in the table below[37]:

Table 27. Apremilast Drug Information

SCIENTIFIC NAME APREMILAST	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMEA	Off label
MHRA	Yes
PMDA	Off label
Indication (ICD-10)	M35.2
Drug Class	Phosphodiesterase-4 Enzyme Inhibitor
Drug Sub-class	Immunomodulating Agent
ATC Code	L04AX06
Pharmacological Class (ASHP)	Phosphodiesterase-4 (PDE-4) inhibitor
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral

Dose (Adult) [DDD]*	Initial: 10 mg PO in the morning on day 1. Titrate upward by additional 10 mg per day on days 2 to 5 as follows: Day 2: 10 mg twice daily; Day 3: 10 mg in the morning and 20 mg in the evening; Day 4: 20 mg twice daily; Day 5: 20 mg in the morning and 30 mg in the evening. Maintenance dose: 30 mg twice daily starting on day 6.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Kidney impairment:** CrCl ≥30 mL/minute: No dosage adjustment necessary. CrCl <30 mL/minute: Initial: 10 mg once daily in the morning on days 1 to 3; titrate using morning doses only (skip evening doses) to 20 mg once daily on days 4 and 5. Maintenance dose: 30 mg once daily in the morning starting on day 6. **Hepatic Impairment:** No dosage adjustment necessary.
Prescribing edits*	ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Apremilast is a reasonable alternative to colchicine (first-line) as a glucocorticoid-sparing agent for patients with recurrent oral ulcers.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common**: diarrhea, nausea, headache, upper respiratory tract infections and fatigue **Most serious**: depression, weight loss, suicidal ideations
Drug Interactions*	**Risk X:** Avoid combination with Strong CYP3A4 Inducers because they may decrease the serum concentration of Apremilast.
Special Population	N/A
Pregnancy	Recommendations for use of apremilast in pregnant patients with rheumatic and musculoskeletal diseases are not available due to lack of data. Placental transfer may be expected based on molecular weight
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Recommendations for use of apremilast in breastfeeding patients with rheumatic and musculoskeletal diseases are not available due to lack of data. Transfer into breast milk may be expected based on molecular weight.
Contraindications	Hypersensitivity to apremilast or any component of the formulation. *Canadian labeling:* Additional contraindications (not in US labeling): Pregnancy; breastfeeding
Monitoring Requirements	Monitor weight regularly during therapy; renal function; signs or symptoms of mood changes, depression, or suicidal thoughts; diarrhea or vomiting, especially patients more susceptible to complications of diarrhea (eg, older patients, patients

	taking medications that may lead to volume depletion or hypotension).
Precautions	Renal impairment: Use with caution in renal impairment. Systemic exposure is increased in patients with severe renal impairment (CrCl <30 mL/minute); dosage reduction is recommended.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Apremilast.**

Table 28. Apremilast HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Apremilast	NICE	Not applicable
	CADTH	Not applicable
	HAS[19]	**Positive Recommendation** – March 16, 2021 Favorable opinion for reimbursement in the treatment of adult patients with oral ulcers associated with Behçet's Disease (BD) only when colchicine is contraindicated, ineffective or poorly tolerated. Opinion unfavorable to reimbursement in other situations.
	IQWIG[20]	**Negative Recommendation** – August 13, 2020 In its dossier assessing the added benefit of apremilast in adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy, the company does not present any suitable data for a comparison with the ACT. Consequently, there is no hint of added benefit of apremilast in comparison with the ACT; an added benefit is therefore not proven.
	PBAC	Not applicable

CONCLUSION STATEMENT- Apremilast

Apremilast is used in the management of Behçet's disease, a condition characterized by recurrent oral and genital ulcers, skin lesions, and inflammation in various parts of the body. The use of colchicine in Behçet's disease is part of the broader treatment approach aimed at controlling inflammation and managing symptoms. Usually given in increasing doses: Initial: 10 mg PO in the morning on day 1. Titrate upward by additional 10 mg per day on days 2 to 5 as follows: Day 2: 10 mg twice daily; Day 3: 10 mg in the morning and 20 mg in the evening; Day 4: 20 mg twice daily; Day 5: 20 mg in the morning and 30 mg in the evening. Maintenance dose: 30 mg twice daily starting on day 6. Its use for Behcet Disease is not backed up by HAS[19] with a positive recommendation supporting its benefit from an economic standpoint. However, it has a negative recommendation from IQWIG[20]. Limitations for the use of Apremilast include depression, weight loss and suicidal ideations.

2.4 Corticosteroids

2.4.1 Prednisone

Information on Prednisone are detailed in the table below[38,39]:

Table 29. Prednisone Drug Information

SCIENTIFIC NAME Prednisone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	M35.2
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB07
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]	**Oral aphthae and genital ulcers:** 15 mg/day (or the equivalent with other

	glucocorticoids), with tapering of the dose to 10 mg/day after one week and discontinuation of prednisone entirely over a two- to three-week period, assuming that the aphthae are no longer symptomatic. Some patients may require higher initial doses. Patients with recurrent oral aphthae may require longer periods of maintenance treatment with low-dose prednisone (eg, 5 mg/day). **Cutaneous lesions:** prednisone (up to 40 mg/day initially) for lesions that are refractory to colchicine. Prednisone doses maintained between 5 and 10 mg/day are usually sufficient to control most skin manifestations of Behçet syndrome. **Arthritis:** Prednisone (10 mg/day) is an appropriate starting dose for the arthritis of Behçet syndrome, but if continuous therapy is required, 5 mg/day or even lower doses should be the target dose, as these doses balance the efficacy and long-term side effects of glucocorticoids well. **Anterior uveitis:** oral prednisone at an initial dose of 40 mg daily. The prednisone may be tapered to discontinuation over one month, assuming prompt disease control. **Posterior uveitis**: start prednisone (1 mg/kg per day for one month, with tapering thereafter as tolerated) **Gastrointestinal manifestations:** Typical starting doses for prednisone for

	gastrointestinal Behçet syndrome are 0.5 to 1 mg/kg daily. The initial dose of glucocorticoids is usually maintained for at least one month or until symptoms improve before the institution of a taper, which is designed to decrease the daily dose to 10 mg/day within two to three months. Subsequent tapering to discontinuation over an additional two months may proceed if disease control is maintained.
Maximum Daily Dose Adults	Usually not to exceed 80 to 100 mg/day but is individualized based on the patient's presentation
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	CU, MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Can be used with immunosuppressive therapies, or other drugs to treat Behcet Disease and its complications
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Prednisone is to be prescribed by a physician who is experienced in the treatment of Behcet Disease (consultant rheumatologist, ophthalmologist, dermatologist)
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Corticosteroids are generally added to first-line treatment options whenever disease management is not optimal
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypertension, tachycardia, nausea.

	Most serious: Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.

Pregnancy	**Pregnancy associated**: Oral: Initial: 10 to 20 mg once daily. Adjust to the minimum effective dose to achieve response; generally, continue for at least 21 days, then taper to the minimum effective dose required to maintain platelet count to prevent major bleeding or 1 mg/kg/day for 2 weeks, followed by a gradual taper. **Fetal alloimmune thrombocytopenia (maternal administration):** Oral: 0.5 to 1 mg/kg/day. Dose is dependent upon gestational age and risk of fetal/neonatal intracranial hemorrhage and is administered in addition to immune globulin IV. Teratogenic effects: Pregnancy Category C Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications	Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections
Monitoring Requirements	Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of

	myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children. **Cardiovascular disease:** Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture. **GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. **Pheochromocytoma:** Pheochromocytoma crisis (may be fatal) has been reported after administration

	of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted. **Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. **Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less

	severe asthmatic episodes in susceptible patients.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Prednisone.**

Table 30. Prednisone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Prednisone	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Prednisone

Prednisone is a corticosteroid that helps to reduce inflammation and control symptoms associated with Behçet's disease during flare-ups. It may be used alone or in combination with other medications, depending on the severity of symptoms and the specific manifestations of the disease in an individual patient. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.

2.4.2 Methylprednisolone

Information on Methylprednisolone are detailed in the table below[39,40]:

Table 31. Methylprednisolone Drug Information

SCIENTIFIC NAME Methylprednisolone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Off-label
EMA	Off-label
MHRA	Off-label
PMDA	Off-label
Indication (ICD-10)	M35.2
Drug Class	Anti-inflammatory Agent
Drug Sub-class	Corticosteroids
ATC Code	H02AB04
Pharmacological Class (ASHP)	Systemic Corticosteroids
DRUG INFORMATION	
Dosage Form	Solution for injection, tablet, powder, and solvent for solution for injection, suspension for injection, lyophilizate for solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]	Initial pulse therapy with intravenous methylprednisolone (1 g/day for three days) is sometimes used empirically for sight-threatening disease.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	CU, MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	Can be used with immunosuppressive therapies, or other drugs to treat Behcet Disease and its complications

G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Methylprednisolone is to be prescribed by a physician who is experienced in the treatment of Behcet Disease (consultant rheumatologist, ophthalmologist, dermatologist)
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Corticosteroids are generally added to first-line treatment options whenever disease management is not optimal
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypertension, tachycardia, nausea. **Most serious:** Adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma, and cataracts.
Drug Interactions*	**Category X:** Aldesleukin BCG (Intravesical) Brivudine Cladribine Desmopressin Disulfiram Fexinidazole Fusidic Acid (Systemic) Indium 111 Capromab Pendetide Lapatinib Macimorelin Methotrimeprazine Mifamurtide MiFEPRIStone Nadofaragene Firadenovec Natalizumab

	Ornidazole Pimecrolimus Rilpivirine Ritlecitinib Ruxolitinib (Topical) Secnidazole Simeprevir Tacrolimus (Topical) Talimogene Laherparepvec Tertomotide
Special Population	**Older adults:** Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth should be routinely monitored in pediatric patients.
Pregnancy	Teratogenic effects: Pregnancy Category C Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications	Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections
Monitoring Requirements	Hemoglobin, occult blood loss, blood pressure, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density;

	intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression.
Precautions	**Adrenal suppression:** May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal axis, particularly in younger children. **Cardiovascular disease:** Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor blood pressure. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture. **GI disease:** Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy. **Hepatic impairment:** Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. **Hepatitis B:** Reactivation may occur. **Ocular disease:** Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. **Pheochromocytoma:** Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the

	risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma. **Renal impairment:** Use with caution in patients with renal impairment; fluid retention may occur. **Seizure disorders:** Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. **Systemic sclerosis:** Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. **Thyroid disease:** Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **Immunizations:** Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted. **Propylene glycol:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. **Sulfite:** Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less

	severe asthmatic episodes in susceptible patients.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Behcet Disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Methylprednisolone.**

Table 32. Methylprednisolone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methylprednisolone	NICE	N/A
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Methylprednisolone

Methylprednisolone may be used in the management of Behcet's disease. The primary goal is to suppress inflammation and alleviate symptoms associated with the condition. The anti-inflammatory and immunosuppressive properties of corticosteroids make them effective in managing the inflammatory processes that occur in Behcet's disease. Corticosteroids can help control symptoms such as oral and genital ulcers, skin lesions, and inflammation of the eyes. Prolonged and high-dose use of corticosteroids may be associated with various side effects, and the goal is often to use the lowest effective dose for the shortest duration necessary to control symptoms. Its use for Behcet Disease is not backed up by any HTA agencies/institutes/authorities. Its use is limited by the heightened risk of developing adrenal suppression (tertiary adrenal insufficiency), Cushing syndrome, hyperglycemia, apathy/depression, peptic ulcers, infections, osteoporosis, glaucoma and cataracts.

2.5 Other Drugs

The following drugs discussed are drugs which are FDA/EMA approved; however, are regarded as non-SFDA registered new molecules.

2.5.1 Interferon-Alfa

Interferon alfa is a type of medication that belongs to the class of interferons, which are proteins that are part of the immune system. Interferon alfa has been studied and used in the treatment of Behçet's disease, a rare and chronic inflammatory disorder that can affect multiple parts of the body, including the eyes, skin, joints, and blood vessels. The off-label use of interferon alfa in Behçet's disease is considered in cases where other treatments may not be effective or are not well-tolerated. Interferon alfa is thought to have immunomodulatory properties, helping to regulate the immune system and reduce inflammation. It is usually given as 5 million units 3 times/week SQ for 6 weeks, followed by 5 million units once a week for 10 weeks. The optimal dose, frequency, and duration of interferon alfa-2b therapy for management of Behçet syndrome is unclear. Caution should be exerced when prescribing this medication because of interferon-alfa cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders[39,41].

2.5.2 Triamcinolone Acetonide

Triamcinolone Acetonide cream is a corticosteroid medication that is sometimes used in the management of Behçet's disease, a chronic and multisystem inflammatory disorder. Topical corticosteroids like triamcinolone acetonide cream may be used for localized skin symptoms in Behçet's disease, such as skin lesions or ulcers. However, the choice of treatment depends on the severity and extent of the disease, and systemic medications are often necessary for more comprehensive control. It was FDA approved on November 29, 2007 for corticosteroid-responsive dermatoses (eg, atopic dermatitis, contact dermatitis, vulvar dermatitis, psoriasis, seborrheic dermatitis). For isolated oral and genital aphthae treatment, it is suggested to have initial treatment with topical corticosteroids such as triamcinolone acetonide cream. It should be applied three to four times daily and be used until pain from the ulcer ceases. Potent topical corticosteroids may also be used for genital ulcers. Prolonged use of topical corticosteroids, especially on large areas of the body or under occlusive dressings, can lead to systemic absorption. This may result in side effects such as adrenal suppression, Cushing's syndrome, and other systemic effects[39,42].

Section 3.0 Key Recommendations Synthesis

The key recommendations are listed below along with their respective levels of evidence:

General Overview:

- Tailor treatment for Behcet's syndrome based on clinical features[8,11].
- Focus on preventing relapses and suppressing inflammation, particularly for major organ involvement[8,11].
- Consider factors such as age, gender, type and severity of organ involvement, disease duration, patient preferences, and organ-specific considerations in treatment decisions[8,11].

Behçet's Disease with Ophthalmic Manifestations:

- Consider anti-TNF therapy such as infliximab (Strong Recommendation, good-quality evidence) or adalimumab (Strong Recommendation, moderate-quality evidence) as first- or second-line corticosteroid-sparing therapy[12].
- Infliximab may be considered for acute exacerbations of pre-existing Behçet's disease (Discretionary Recommendation, insufficient-quality evidence)[12].
- Etanercept may be considered for patients intolerant to infliximab and adalimumab. (Discretionary Recommendation, insufficient-quality evidence)[12].
- **Uveitis Management:** Treatment options include:
  - azathioprine (Level of evidence IA, strength of recommendation A/B)
  - cyclosporine-A (Level of evidence IB, strength of recommendation A/B)
  - interferon-alpha (Level of evidence IIA, strength of recommendation A/B)
  - monoclonal anti-TNF antibodies (Level of evidence IIA, strength of recommendation A/B)[8].
- Systemic corticosteroids and immunosuppressive therapy are essential for every case of posterior uveitis in Behçet's disease. Severe cases may require the introduction of corticosteroids and anti-TNFα. Interferon-α is an alternative therapeutic option[10].

Mucocutaneous Involvement:

- **Oral and Genital Ulcers:** Topical steroids are recommended. Colchicine is the initial choice for preventing recurrent mucocutaneous lesions (Level of evidence IB, Strength of recommendation A)[8,11,21].

- Colchicine serves as the first-line treatment for mucocutaneous and articular manifestations, with a recommended duration of 3–6 months at a posology of 1–2 mg/day[10].
- Alternative drugs include thalidomide, dapsone, azathioprine, apremilast, interferon-alpha, and etanercept. Novel choices like interleukin-1 and interleukin-17 inhibitors may be effective[11].
- Apremilast for oral aphthous ulcers is likely to be effective, and its administration is recommended (Evidence level: 1b, Grade of recommendation: B)[21].
- Use of antimicrobial agents is proposed for oral ulcers in the absence of lesions in major organs. For those with major organ involvement, combination with colchicine is suggested (Evidence level: 3, Grade of recommendation: C1)[21].
- **Papulopustular Lesions:** Managed using topical or systemic measures similar to acne vulgaris (Level of evidence IV, Strength of recommendation D)[8].
- **Leg Ulcers:** Collaboration with dermatologists and vascular surgeons is advised. Consideration of azathioprine, thalidomide, interferon-alpha, TNF-alpha inhibitors, or apremilast in selected cases (Level of evidence IB, Strength of recommendation A)[8].
- **Erythema Nodosum:** recommend topical steroids (C1, level of evidence 6), NSAIDs, minocycline (C1, level of evidence 4), dapsone (C1, level of evidence 1b), colchicine (B, level of evidence 1b) and TNF-a inhibitors for severe erythema nodosum (C1, level of evidence 1b)[21].
- **Acneiform Eruptions in Behcet's Disease:** topical steroids (C1, level of evidence 6), oral antimicrobial agents (C1, level of evidence 5) and oral colchicine (B, level of evidence 2) are recommended for the treatment[21].

Acute Deep Vein Thrombosis:

- Glucocorticoids and immunosuppressives such as azathioprine, cyclophosphamide, or cyclosporine-A are recommended (Level of evidence III, Strength of recommendation C)[8,15].
- Anticoagulants should be considered as a treatment option for deep vein thrombosis, except in patients at high risk of bleeding (Strength of recommendation C1, Evidence level 5)[15].

Refractory Venous Thrombosis:

- **Monoclonal Anti-TNF Antibodies:** Consideration in refractory patients. Anticoagulants may be added with caution (Level of evidence III, Strength of recommendation C)[8].

- Inflammatory venous thromboses justify systemic anti-inflammatory treatment with corticosteroids and possibly immunosuppressants or immunomodulators. Anticoagulant use is debated but may be considered in adults during the acute phase, especially with associated arterial aneurysms[10,11].

Arterial Involvement:

- **Pulmonary Artery Aneurysms:** High-dose glucocorticoids and cyclophosphamide. Monoclonal anti-TNF antibodies in refractory cases (Level of evidence III, Strength of recommendation C)[8,11,15].
- **Nonpulmonary Aneurysms:** Corticosteroids are strongly recommended, coupled with immunosuppressants like cyclophosphamide and azathioprine (Strength of recommendation A, Evidence level 4)[15].
- **Aortic and Peripheral Artery Aneurysms:** Medical treatment with cyclophosphamide and corticosteroids before intervention. Surgery or stenting should not be delayed in symptomatic patients (Level of evidence III, Strength of recommendation C)[8].
- **Valvular and Aortic Involvement:**
    - Severe Aortic Regurgitation: Warrants prosthetic valve replacement.
    - Aortic Root Involvement: Aortic root replacement is recommended.
    - Thoracic and Abdominal Aortic Aneurysms: Graft replacement advised based on risk factors (size, enlargement speed, and shape). (Strength of recommendation C1, Evidence level 4)[15].

Nervous System Involvement:

- Initiate colchicine (1.0-2.0 mg/day) immediately after the first attack and continue for 5 years (Strength of recommendation B, Level of evidence 3)[22].
- **Acute Parenchymal Involvement:** High-dose glucocorticoids, followed by gradual tapering, and immunosuppressives like azathioprine. Monoclonal anti-TNF antibodies considered in severe cases (Level of evidence III, Strength of recommendation C)[8,11].
- A typical glucocorticoid regimen would be starting with daily pulses of intravenous methylprednisolone 1 g/day that may be continued for up to 7 days followed by oral prednisolone (or prednisone) at 1mg/kg/day for 1month and tapered by 5–10mg every 10–15 days[8].
- If corticosteroids at a moderate or higher dose are insufficient, consider concurrent use of infliximab (Strength of recommendation C1, Level of evidence 5)[22].

- Consider interferon-alpha or tocilizumab for refractory cases[11].
- **Cerebral Venous Thrombosis:** The first episode of cerebral venous thrombosis should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration with careful exclusion of arterial aneurysms. Screening for vascular disease is crucial (Level of evidence III, Strength of recommendation C)[8,11].

Joint Involvement:

- **Acute Arthritis:** Initial treatment with colchicine. Intra-articular glucocorticoids for acute monoarticular disease. Corticosteroids and NSAIDs are considered for acute exacerbations[8,11].
- Recurrent and chronic cases may benefit from azathioprine, interferon-alpha, TNF-alpha inhibitors (adalimumab and infliximab) or etanercept (Level of evidence IB, Strength of recommendation A)[8,11].

Consider conventional DMARDs and secukinumab for chronic courses resembling spondyloarthropathies[11].**Gastrointestinal Involvement:**

- Use glucocorticoids during acute exacerbations with disease-modifying agents (sulfasalazine, azathioprine)[11].
- **For mild to moderate cases:** consider the use of 5-ASA and salazosulfapyridine (Evidence level: 5, Recommendation: A)[9].
- **For moderate to severe cases:** consider the use of corticosteroids, TNF inhibitors, and nutrition therapy (Evidence level: 5, Recommendation: A)[9].
- **For severe refractory/severe gastrointestinal Involvement: Urgent Surgical Consultation:** Essential for perforation, major bleeding, or obstruction. Consider glucocorticoids, disease-modifying agents, monoclonal anti-TNF antibodies, and/or thalidomide (Level of evidence III, Strength of recommendation C)[8,11].
- **For Remission Maintenance:** Consider 5-ASA drugs, thiopurine drugs, TNF inhibitors, and nutrition therapy (Evidence level: 5, Recommendation: A)[9].
- Methotrexate is not recommended as a sole treatment for intestinal BD (Evidence level: 6, Recommendation: A)[9].
- **Nutrition**: Consider Enteral Nutrition as an additional treatment for refractory cases. The use of Total Parenteral Nutrition is not clear; recommend only in severe disease cases and for a limited period (Evidence level: 6, Recommendation: B)[9].

- **Surgical Treatment:**
  - Perform in cases of absolute indications such as intestinal perforation, severe stricture, large abscess, and massive gastrointestinal bleeding.
  - Consider for relative indications like refractory cases with a low quality of life due to complications such as fistula (Evidence level: 4, Recommendation: A)[9].
- **Pediatric Patients:** Treat similar to adult patients but minimize corticosteroid use to avoid growth disturbance (Evidence level: 6, Recommendation: A)[9].

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Behcet Disease.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Filters	Search Details	Results
((((((((((((Behcet Syndrome[MeSH Terms]) OR (Behcet's Syndrome[Title/Abstract])) OR (Triple-Symptom Complex[Title/Abstract])) OR (Triple Symptom Complex[Title/Abstract])) OR (Symptom Complex, Triple[Title/Abstract])) OR (Triple Symptom Complices[Title/Abstract])) OR (Behçet Disease[Title/Abstract])) OR (Behçet Diseases[Title/Abstract])) OR (Adamantiades-Behcet Disease[Title/Abstract])) OR (Adamantiades Behcet Disease[Title/Abstract])) OR (Adamantiades-Behcet Diseases[Title/Abstract])) OR (Behcet Triple Symptom Complex[Title/Abstract])) OR (Old Silk Route Disease[Title/Abstract])) OR (Behcet's Disease[Title/Abstract])) OR (Behcet Disease[Title/Abstract])	Guideline, in the last 5 years	("behcet syndrome"[MeSH Terms] OR "behcet s syndrome"[Title/Abstract] OR "triple symptom complex"[Title/Abstract] OR "triple symptom complex"[Title/Abstract] OR (("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "Symptom"[All Fields] OR "symptom s"[All Fields] OR "symptomes"[All Fields]) AND "complex triple"[Title/Abstract]) OR "behcet disease"[Title/Abstract] OR "behcet diseases"[Title/Abstract] OR "adamantiades behcet disease"[Title/Abstract] OR "adamantiades behcet disease"[Title/Abstract] OR ("Adamantiades-Behcet"[All Fields] AND "Diseases"[Title/Abstract]) OR (("Behcet"[All Fields] OR "Behcet's"[All Fields] OR "behcets"[All Fields]) AND "triple symptom complex"[Title/Abstract]) OR "old silk route disease"[Title/Abstract] OR "behcet s disease"[Title/Abstract] OR "behcet disease"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	1

Appendix C. Treatment Algorithm

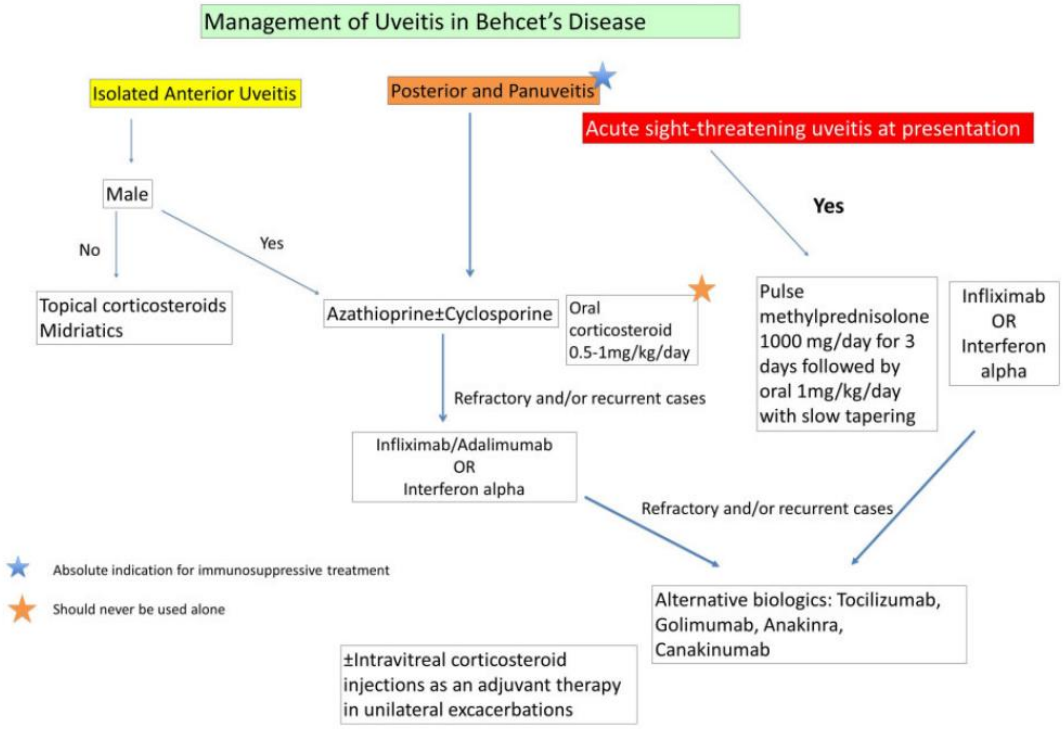
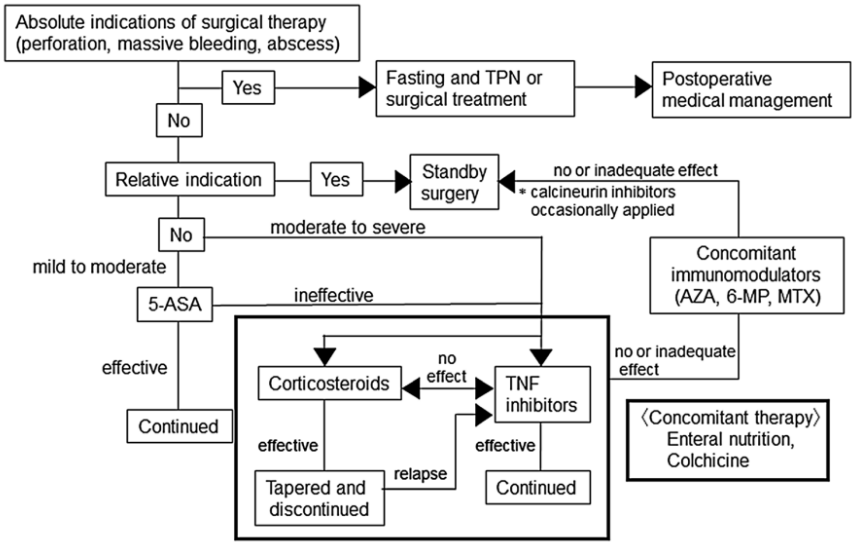
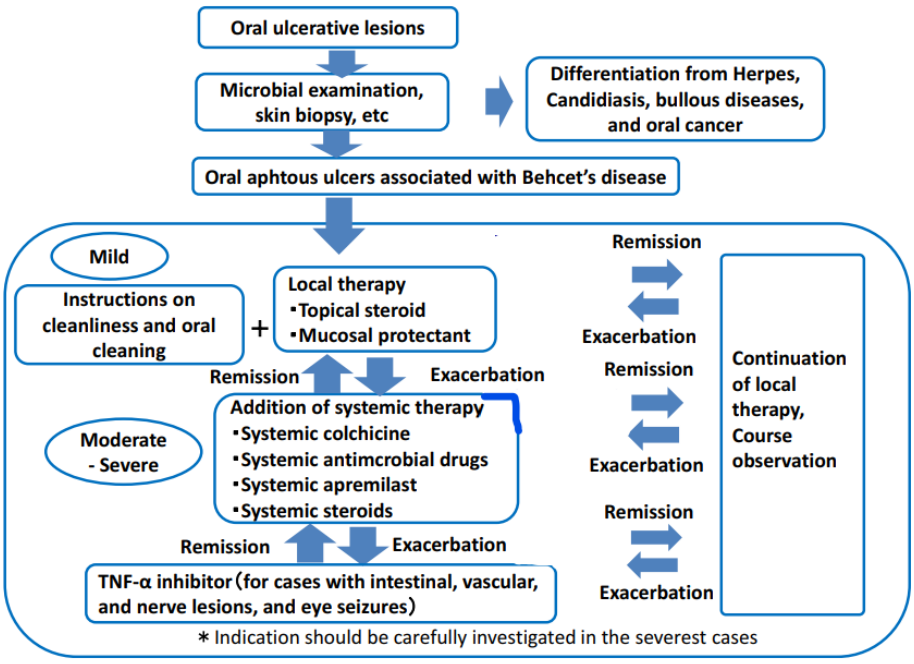


Figure 1. *Algorithm for the management of Behcet's syndrome*



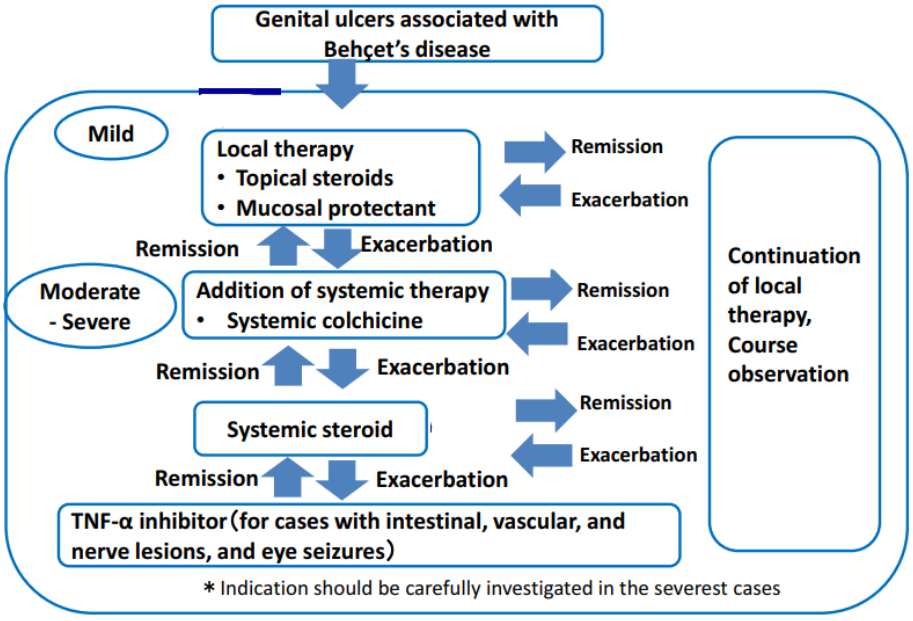
5- ASA 5-aminosalicylic acid, 6- MP 6-mercaptopurine, AZA azathioprine, MTX methotrexate, TNF tumor necrosis factor, TPN total parenteral nutrition

Figure 2. *Algorithm for the treatment of intestinal BD*



TNF, tumor necrosis factor

Figure 3. *Algorithm of treatment for oral aphthous ulcers*



TNF, tumor necrosis factor

Figure 4. *Algorithm of treatment for genital ulcers*