Azathioprine toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Azathioprine must be at a dose of at least 1 mg/kg per day

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3 x 10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50 x 10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0 x 10^9/L	3 (or higher)
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Neurology / Senses		
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Pulmonary		
Pneumonitis/pulmonary infiltrates	Radiographic changes, Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Other		
Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fatigue, malaise	Severe, loss of ability to perform some activities	3 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)
Infection	Severe, systemic infection, requiring IV antimicrobial treatment or hospitalisation	3 (or higher)
Secondary malignancy	Secondary malignancy present	4

Cyclosporin toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Cyclosporin must be at a dose of at least 2mg/kg/day

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3 x 10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50 x 10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0 x 10^9/L	3 (or higher)
Cardiovascular		
Hypertension	Recurrent / persistent rise of > 20 mmHg diastolic BP or rise to > 150/90 on two occasions if BP previously normal	2 (or higher)
Fluid retention	Symptomatic, limiting function, unresponsive to therapy or requiring drug discontinuation	3 (or higher)
Dermatology / Skin		
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Weight gain / loss	20% or more weight gain or loss	3 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Musculoskeletal		
Muscle weakness	Symptomatic and interfering with function	2 (or higher)
Neurology / Senses		
Ataxia (incoordination)	Mild symptoms interfering with function but not interfering with activities of daily living	2 (or higher)
Decreased level of consciousness	Somnolence or sedation interfering with function but not interfering with activities of daily living	2 (or higher)
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Hearing	Tinnitus or hearing loss not requiring hearing aid or treatment	2 (or higher)
Mood alteration	Moderate mood alteration interfering with function but not interfering with activities of daily living	2 (or higher)
Neuropathy - Sensory	Objective sensory loss or paraesthesia interfering with function but not interfering with activities of daily living	2 (or higher)
Seizure(s)	Seizures in which consciousness is altered	3 (or higher)
Vision	Symptomatic and interfering with function but not interfering with activities of daily living	2 (or higher)
Renal		
Haematuria	Macroscopic (or dipstick +++) confirmed on two separate occasions	2 (or higher)
Proteinuria	> 1.0g/24 hours, elevated urine protein/creatinine ratios, (dipstick protein ++ or greater), confirmed on two separate occasions	2 (or higher)
Renal impairment	Creatinine > 1.5 ULN or creatinine clearance < 30mL/min	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade

Other

Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fatigue, malaise	Severe, loss of ability to perform some activities	3 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)
Hyperkalaemia	Potassium > 6 mmol/L	3 (or higher)
Infection	Severe, systemic infection, requiring IV antimicrobial treatment or hospitalisation	3 (or higher)
Secondary malignancy	Secondary malignancy present	4

Sodium aurothiomalate toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Sodium aurothiomalate must be at a dose of at least 50mg weekly

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade

Blood / Bone Marrow

Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Eosinophilia	Persistent / unexplained eosinophilia > 1×10^9/L	
Leukopenia	Total WCC < 3×10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50×10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0×10^9/L	3 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Neurology / Senses		
Decreased level of consciousness	Somnolence or sedation interfering with function but not interfering with activities of daily living	2 (or higher)
Neuropathy - Sensory	Objective sensory loss or paraesthesia interfering with function but not interfering with activities of daily living	2 (or higher)
Seizure(s)	Seizures in which consciousness is altered	3 (or higher)
Syncope (fainting)	Present	3 (or higher)
Vision	Symptomatic and interfering with function but not interfering with activities of daily living	2 (or higher)
Vision – cornea / retina	Symptomatic corneal and / or lenticular changes present	1 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade

Pulmonary

Cough (severe)	Severe cough or coughing spasm, poor control or unresponsive to treatment. Evidence of reversal on cessation of treatment.	3 (or higher)
Pneumonitis/pulmonary infiltrates	Radiographic changes, Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary fibrosis	Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary symptoms - new or worsening (probable drug-induced pneumonitis)	Development of syndrome consistent with drug-induced pneumonitis (eg cough, dyspnoea, fever, hypoxaemia etc) with lung infiltrates on imaging (refer Searles McKendry criteria)	

Renal

Haematuria	Macroscopic (or dipstick +++) confirmed on two separate occasions	2 (or higher)
Proteinuria	> 1.0g/24 hours, elevated urine protein/creatinine ratios, (dipstick protein ++ or greater), confirmed on two separate occasions	2 (or higher)
Renal impairment	Creatinine > 1.5 ULN or creatinine clearance < 30mL/min	2 (or higher)

Other

Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)

Hydroxychloroquine toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Hydroxychloroquine must be at a dose of at least 200mg daily

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3 x 10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50 x 10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0 x 10^9/L	3 (or higher)
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Musculoskeletal		
Muscle weakness	Symptomatic and interfering with function	2 (or higher)
Neurology / Senses		
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Hearing	Tinnitus or hearing loss not requiring hearing aid or treatment	2 (or higher)
Neuropathy - Motor	Objective weakness interfering with function but not interfering with activities of daily living	2 (or higher)
Seizure(s)	Seizures in which consciousness is altered	3 (or higher)
Vision	Symptomatic and interfering with function but not interfering with activities of daily living	2 (or higher)
Vision – cornea / retina	Symptomatic corneal and / or retinal changes present	1 (or higher)
Other		
Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)

Leflunomide toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Leflunomide must be at a dose of at least 10mg daily

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3 x 10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50 x 10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0 x 10^9/L	3 (or higher)
Cardiovascular		
Arrhythmia	Symptomatic and requiring therapy	3 (or higher)
Hypertension	Recurrent / persistent rise of > 20 mmHg diastolic BP or rise to > 150/90 on two occasions if BP previously normal	2 (or higher)
Fluid retention	Symptomatic, limiting function, unresponsive to therapy or requiring drug discontinuation	3 (or higher)
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Weight gain / loss	20% or more weight gain or loss	3 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Neurology / Senses		
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Mood alteration	Moderate mood alteration interfering with function but not interfering with activities of daily living	2 (or higher)
Vision	Symptomatic and interfering with function but not interfering with activities of daily living	2 (or higher)
Pulmonary		
Cough (severe)	Severe cough or coughing spasm, poor control or unresponsive to treatment. Evidence of reversal on cessation of treatment.	3 (or higher)
Pneumonitis/pulmonary infiltrates	Radiographic changes, Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary fibrosis	Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary symptoms - new or worsening (probable drug-induced pneumonitis)	Development of syndrome consistent with drug-induced pneumonitis (eg cough, dyspnoea, fever, hypoxaemia etc) with lung infiltrates on imaging (refer Searles McKendry criteria)	

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Renal		
Haematuria	Macroscopic (or dipstick +++) confirmed on two separate occasions	2 (or higher)
Proteinuria	> 1.0g/24 hours, elevated urine protein/creatinine ratios, (dipstick protein ++ or greater), confirmed on two separate occasions	2 (or higher)
Renal impairment	Creatinine > 1.5 ULN or creatinine clearance < 30mL/min	2 (or higher)
Other		
Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fatigue, malaise	Severe, loss of ability to perform some activities	3 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)
Hypokalaemia	Potassium < 3 mmol/L	3 (or higher)
Infection	Severe, systemic infection, requiring IV antimicrobial treatment or hospitalisation	3 (or higher)
Secondary malignancy	Secondary malignancy present	4

Methotrexate toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Methotrexate must be at a dose of at least 20mg weekly

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3 x 10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50 x 10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0 x 10^9/L	3 (or higher)
Cardiovascular		
Pericardial effusion /pericarditis	Pericarditis (pericardial rub, ECG changes or chest pain)	2 (or higher)
Thrombosis / embolism	Requiring anticoagulant therapy	3 (or higher)
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased, and symptoms do not improve with at least two of the following measures: 1. Reduction of the methotrexate dose 2. Folinic acid / folic acid supplementation 3. Switching from oral to intramuscular dosing 4. Dividing the methotrexate dose over 12 hours A minimum of three doses of methotrexate should have been trialled	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)
Musculoskeletal		
Osteonecrosis (avascular necrosis)	Symptomatic and interfering with function	2 (or higher)
Osteoporosis	Symptomatic and requiring treatment	3 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Neurology / Senses		
Decreased level of consciousness	Somnolence or sedation interfering with function but not interfering with activities of daily living	2 (or higher)
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Hearing	Tinnitus or hearing loss not requiring hearing aid or treatment	2 (or higher)
Mood alteration	Moderate mood alteration interfering with function but not interfering with activities of daily living	2 (or higher)
Seizure(s)	Seizures in which consciousness is altered	3 (or higher)
Vision	Symptomatic and interfering with function but not interfering with activities of daily living	2 (or higher)
Pulmonary		
Cough (severe)	Severe cough or coughing spasm, poor control or unresponsive to treatment. Evidence of reversal on cessation of treatment.	3 (or higher)
Pneumonitis/pulmonary infiltrates	Radiographic changes, Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary fibrosis	Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary symptoms - new or worsening (probable drug-induced pneumonitis)	Development of syndrome consistent with drug-induced pneumonitis (eg cough, dyspnoea, fever, hypoxaemia etc) with lung infiltrates on imaging (refer Searles McKendry criteria)	
Renal		
Haematuria	Macroscopic (or dipstick +++) confirmed on two separate occasions	2 (or higher)
Renal impairment	Creatinine > 1.5 ULN or creatinine clearance < 30mL/min	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Other		
Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fatigue, malaise	Severe, loss of ability to perform some activities	3 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)
Infection	Severe, systemic infection, requiring IV antimicrobial treatment or hospitalisation	3 (or higher)
Nodulosis (following introduction of methotrexate therapy)	Development of multiple new nodules causing significant local pressure symptoms and distress to patient	
Secondary malignancy	Secondary malignancy present	4

Sulfasalazine toxicity criteria and severity descriptors for the listing of biological agents for rheumatoid arthritis on the PBS

Only valid for adult patients

Sulfasalazine must be at a dose of at least 2g daily

ULN = upper limit of normal

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Blood / Bone Marrow		
Anaemia	Haemoglobin < 80 g/L	3 (or higher)
Leukopenia	Total WCC < 3×10^9/L	2 (or higher)
Thrombocytopenia	Platelets < 50×10^9/L	3 (or higher)
Neutropenia	Total neutrophils < 1.0×10^9/L	3 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Dermatology / Skin		
Alopecia	Pronounced hair loss	2 (or higher)
Rash / desquamation	Scattered macular or papular eruption or erythema **with pruritis or other associated symptoms** covering < 50% of body surface or localised desquamation or other lesions covering < 50% of body	2 (or higher)
Gastrointestinal		
Diarrhoea	Increase of 4-6 stools/day over pre-treatment	2 (or higher)
Nausea	Oral intake significantly decreased	2 (or higher)
Pancreatitis	Abdominal pain with pancreatic enzyme elevation	3 (or higher)
Stomatitis	Painful erythema, oedema or ulcers but able to eat or swallow	2 (or higher)
Vomiting	2 or more episodes per 24 hours over pre-treatment	2 (or higher)
Hepatic		
Bilirubin	> 1.5 x ULN	2 (or higher)
Transaminases	ALT and/or AST > 2.5 x ULN **or** ALT and/or AST > 1.5 x ULN on three occasions over a three month period	2 (or higher)
↑ Serum alkaline phosphatase	2.5 x ULN	2 (or higher)

Adverse event	Brief description of minimum grade	NIH common toxicity criteria grade
Neurology / Senses		
Headaches (severe)	Severe pain : pain or analgesics severely interfere with activities of daily living	3 (or higher)
Hearing	Tinnitus or hearing loss not requiring hearing aid or treatment	2 (or higher)
Mood alteration	Moderate mood alteration interfering with function but not interfering with activities of daily living	2 (or higher)
Neuropathy - Sensory	Objective sensory loss or paraesthesia interfering with function but not interfering with activities of daily living	2 (or higher)
Seizure(s)	Seizures in which consciousness is altered	3 (or higher)
Pulmonary		
Cough (severe)	Severe cough or coughing spasm, poor control or unresponsive to treatment. Evidence of reversal on cessation of treatment.	3 (or higher)
Pneumonitis/pulmonary infiltrates	Radiographic changes, Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Pulmonary fibrosis	Respiratory Function Test abnormalities and requiring steroids or diuretics	2 (or higher)
Renal		
Haematuria	Macroscopic (or dipstick +++) confirmed on two separate occasions	2 (or higher)
Proteinuria	> 1.0g/24 hours, elevated urine protein/creatinine ratios, (dipstick protein ++ or greater), confirmed on two separate occasions	2 (or higher)
Renal impairment	Creatinine > 1.5 ULN or creatinine clearance < 30mL/min	2 (or higher)
Other		
Allergic reaction	Urticaria, drug fever > 38°C and / or bronchospasm	2 (or higher)
Fever (in the absence of neutropenia)	Body temp > 39°C (oral or tympanic)	2 (or higher)