Supplementary tables for systemic non-biologic treatment of psoriasis pathway

List of supplementary tables

***Table 1**. Baseline Screening, monitoring, and labs for systemic non-biologic and treatment of psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Baseline screening, monitoring, and labs	• History and physical examination • Lipid profile, CBC, LFT, renal function tests • Pregnancy test if indicated		• History and physical examination • BP x 2 • BUN and SCr • Urinalysis • Consider latent TB test • LFT, CBC, lipid profile, magnesium, uric acid, and potassium • Pregnancy test if indicated	• History and physical examination • CBC • Serum chemistry screen • Urinalysis	• History and physical examination • TB and hepatitis B and C • Non-invasive baseline liver fibrosis assessment (Fibrotest®, Fibrosure®, Fibrometer®, or Hepascore®) <u>Additional monitoring recommended for patients with impaired kidney function</u> • BUN and SCr Check • CBC 5-7 days after a test-dose	• CBC with diff., CMP, and lipid profile • TB, hepatitis B and C, and HIV • Vaccination with recombinant zoster vaccine prior to initiation of therapy should be considered

* Not FDA approved for psoriasis in the US

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus*
Baseline screening, monitoring, and labs	• History and physical examination • TPMT level prior to initiation of therapy • LFT, CBC with differential, CMP, and urinalysis • TB and hepatitis B and C screen • Pregnancy test if indicated	• History and physical examination • CBC • Pregnancy test if indicated	• History and physical examination • CBC with differential and LFT • Pregnancy test if indicated	• History and physical examination • CBC, serum chemistry, and LFT • Pregnancy test if indicated	• History and physical examination • CBC, CMP, LFT • Hepatitis B and C and TB screen • Pregnancy test if indicated	• History and physical examination • CBC with differential • Pregnancy test if indicated

***Table 2**. Ongoing monitoring for systemic non-biologic treatment of psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Ongoing monitoring	• LFT and lipid profile monthly for the first 3 months, then every 3 months • CBC count, renal function tests every 3 months • Pregnancy test if indicated	• Routine laboratory screening and monitoring can be considered on an individual basis. • Weight should be monitored regularly, and if weight loss occurs (> 5% from baseline), discontinuation of apremilast should be considered	• Monitor BP, BUN, and SCr biweekly during the first 3 months and then monthly if no persistent abnormalities are identified • Monthly CBC, LFT, lipid profile, magnesium, uric acid, and potassium • Pregnancy testing if indicated • Weekly blood pressure	• CBC biweekly for the first 2 months; monthly until 6 months; and bimonthly thereafter	• Monitor CBC every 3-6 months, assuming no abnormal laboratory results • LFT every 3-6 months • Periodic renal monitoring for patients with poor renal function • Liver evaluation if used long-term	• CBC with differential, CMP, and lipid profile at 4-8 weeks after the initiation, then every 3 months thereafter

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus†*
Ongoing monitoring	• CBC with differential biweekly for the first 2 months, monthly for the next 2 months, every 2 months thereafter • LFT monthly for the first 3 months, then every 2 months thereafter • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy testing if indicated	• Weekly CBC until a stable dose is achieved, then monthly • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy testing if indicated	• Monthly CBC with differential and LFT for the first 6 months and every 6-8 weeks thereafter • Pregnancy testing if indicated	• CBC weekly for 1 month; every 2 weeks thereafter for 2 months; then monthly thereafter • Monthly CMP and LFT • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy testing if indicated	• CBC every 2-4 weeks; CMP every 3 months • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy test if indicated	• BP • Serum chemistry • Renal function test • LFT • Pregnancy test if indicated

† *Proper monitoring frequency is not established*

Table 3. *Adverse effects for systemic non-biologic treatment of psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Adverse effects	• Cheilitis • Alopecia • Xerosis • Pruritus • Xerophthalmia • Night blindness • Dry Mouth • Paronychia • Paresthesia • Headache • Pseudotumor cerebri • Nausea • Abdominal pain • Joint pain • Myalgia • Hypertriglyceridemia • Abnormal LFT • Teratogenecity	• Diarrhea, nausea, upper respiratory tract infections, and headache • Dehydration and its complications in > 65 years • Emergence or worsening of depression • Weight loss	• Renal impairment (acute & chronic) • Hypertension • Malignancies • Headache, tremor, and paresthesia • Hypertrichosis • Gingival Hyperplasia • Worsening acne • Nausea, vomiting, and diarrhea • Myalgias • Flu-like symptoms • Lethargy • Hypertriglyceridemia • Hyperkalemia • Hyperbilirubinemia • Increased risk of infections	• Anaphylaxis/ angioedema • Abdominal cramps, nausea, diarrhea, fullness, and flatulence • Flushing • Malaise • Fatigue • Lymphopenia, leukopenia, eosinophilia • Hepatotoxicity and elevated LFT • Increased cholesterol, triglycerides • Increased serum creatinine, potassium, and proteinuria • Possible renal disease	• Fatigue • Anorexia • Nausea • Stomatitis • Pneumonitis • Myelosuppression • Epidermal necrolysis • Hepatotoxicity • Hematologic toxicity	• Nasopharyngitis • Infections • Blood clots • Malignancies • Abnormal LFT, lipid, and creatinine levels • Lymphopenia, neutropenia, and anemia

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus*
Adverse effects	• Bone-marrow suppression • Malignancies • Cutaneous SCCs • Lymphoproliferative disorders • Increased risk of infections • Nausea, vomiting, and diarrhea • Hypersensitivity syndrome • Pancreatitis • Hepatitis	• Bone-marrow suppression • Stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation • Rash, ulceration, dermatomyositis-like skin changes, and alopecia • Dysuria (rare) • Headache, dizziness, disorientation, hallucinations, and convulsions • Temporary impairment of renal tubular function accompanied by elevated serum uric acid, BUN, and creatinine • Fever, chills, malaise, edema, and asthenia • Elevated LFT • Pulmonary fibrosis	• Most common adverse effects include nausea, diarrhea, loss of appetite, weight loss, headache, dizziness • Severe liver injury • Pancytopenia, agranulocytosis, and thrombocytopenia in patients treated with or who had recently discontinued methotrexate or other immunosuppressive agents	• GI adverse effects (diarrhea, nausea/vomiting, abdominal cramps); occur early and decrease with continued use • Hematologic (leukopenia, anemia, and thrombocytopenia) • Genitourinary (urgency, frequency, dysuria, and sterile pyuria) • Susceptibility to viral, bacterial, and mycobacterial infections • Progressive multifocal leukoencephalopathy • Hypercholesterolemia, hypophosphatemia, hyperkalemia, hypokalemia • Fever and myalgias • Headache, insomnia • Peripheral edema • Hypertension	• Myelosuppression • Liver toxicity from hepatic veno-occlusive disease • Increased ALT and AST • Hyperuricemia • Photodermatitis • Taste changes • Gastroesophageal reflux, gastric ulcers • Headache • Nausea/vomiting • Aphthous ulcers • Fatigue • Nonmelanoma skin cancer • Verrucae vulgaris, herpes zoster	• Common: tremor, headache, nausea, diarrhea, hypertension, and abnormal renal function test • Less common: hyperglycemia, hyperkalemia, elevated LFT, anemia, leukocytosis, dyspnea, fever, arthralgias, edema, diabetes, insomnia, paresthesia

Table 4. *Contraindications for non-biologic systemic therapy for psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Contraindications	• Acitretin is a potent teratogen in women of childbearing potential • Females of childbearing potential cannot consider pregnancy up to 3 years after completion of treatment. • Severely impaired liver or kidney function • Chronic abnormally elevated blood lipid levels	• Known hypersensitivity to apremilast • Do not use with cytochrome P450 enzyme inducers	• Prior PUVA treatment (especially >200 treatments) or radiation therapy • Abnormal renal function • Uncontrolled hypertension • Malignancy • Hypersensitivity to cyclosporine • Live vaccinations should be avoided • Caution with major infections and poorly controlled diabetes	• Severe liver disease • Severe or chronic GI disease • Severe or chronic kidney disease • Malignancy or a history of malignancy • Leukopenia and other hematologic abnormalities • Pregnancy • Breast-feeding	**Absolute:** • Pregnancy • Nursing • Alcoholism • Alcoholic liver disease or other chronic liver diseases • Immunodeficiency syndromes • Bone-marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia • Hypersensitivity to methotrexate **Relative:** • Abnormalities in renal function • Abnormalities in liver function • Active infection	• Tofacitinib should not be initiated if the: ○ Absolute lymphocyte count < 500 cells/mm^2 ○ Absolute Neutrophil Count (ANC) < 1000 cells/mm^2 ○ Hemoglobin < 9g/dL • Severe hepatic impairment • Active serious infections

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus*
Contraindications	**Absolute** • Allergy to azathioprine • Pregnancy or attempting pregnancy • Clinically significant active infection **Relative** • Concurrent use of allopurinol • Prior treatment with cyclophosphamide or chlorambucil	• Marked bone-marrow suppression, including leukopenia, thrombocytopenia, or anemia	• Patients with hypersensitivity to leflunomide or its metabolites	• Hypersensitivity to mycophenolate mofetil (MMF) and mycophenolic acid	• Pre-existing liver disease • Immunosuppression • Anemia, leukopenia, or thrombocytopenia	• Hypersensitivity to tacrolimus or its metabolites

Table 5. *Vaccines and systemic non biologic treatment for psoriasis*

	Acitretin	**Apremilast**	**Cyclosporine**	**Fumaric acid esters**	**Methotrexate**	**Tofacitinib**
Vaccines			• Live vaccinations should be avoided • May have a drug interaction with killed or recombinant vaccines			
	Azathioprine	**Hydroxyurea**	**Leflunomide**	**Mycophenolate mofetil***	**Thioguanine**	**Tacrolimus**
Vaccines				Live attenuated vaccines should not be given during the treatment		

Table 6. *Pregnancy and Nursing during Systemic Biologic-treatment for Psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Pregnancy & Nursing	• Should not be used by patients who are pregnant or intend to become pregnant for at least 3 years following discontinuation of therapy • Mothers receiving acitretin should not breastfeed	• Should only be used in pregnancy if the benefit justifies the potential risk to the fetus	• Lower birth weight and shorter duration of pregnancy reported in patients with transplantation; appears not to be teratogenic in patients with transplantation • Cyclosporine is present in breast milk; a decision should be made whether to discontinue nursing or cyclosporine based on the benefit of therapy to the patient	• Should not be used during pregnancy or nursing	• Should not be used during pregnancy or nursing	• Tofacitinib can be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus*
Pregnancy & Nursing	• Should not be used during pregnancy and nursing	• Should not be used during pregnancy and nursing	• Should not be used during pregnancy and nursing	• Should not be used during pregnancy and nursing	• Should not be used during pregnancy and nursing	• It can be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus • Should not be used during nursing

***Table 7**. Dosing for non-biologic systemic therapies for psoriasis treatment*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters*	Methotrexate	Tofacitinib*
Dosing	• 10-50 mg/d given as a single dose • Lower doses (≤ 25 mg/d) are often used to minimize adverse effects, especially in combination regimens • When acitretin is added to UV, the light dose should be reduced by 30%-50%	• Patients should initially start at a lower dose (10 mg) which is titrated up over five days to reduce the risk of GI AEs. Thereafter, apremilast is dosed 30 mg by mouth twice daily. • Dosage Titration Schedule: ○ Day 1 – 10 mg (AM) ○ Day 2 – 10 mg (AM & PM) ○ Day 3 – 10 mg (AM); 20 mg (PM) ○ Day 4 – 20 mg (AM & PM) ○ Day 5 – 20 mg (AM); 30 mg (PM) ○ Day 6 –: 30 mg (AM & PM) • 30 mg once daily in patients with severe renal impairment (creatine clearance < 30 mL/min)	• 2.5-5.0 mg/kg/d in two divided doses/day • Dose adjustments downward (by 0.25-1.0 mg/kg) when clearance of psoriasis is achieved or when hypertension or decreased renal function are observed • US approval: 1 y continuous treatment • Optimally used as interventional therapy; may be repeated at intervals after a rest period	• One pill of lower strength (105 mg of fumaric acid ester mixtures) and then escalate over 8 weeks to 6 pills of regular strength (215 mg of fumaric acid ester mixtures), as tolerated	• 7.5 -25 mg weekly as a single dose or in three doses over 24 hours • A test dose should be considered, especially in patients with impaired kidney function • Administration of folic acid or folinic acid is recommended to reduce the incidence of GI and hepatic adverse effects.	• 5-10 mg twice daily • 5mg once daily for moderate to severe renal or hepatic impairment

	Azathioprine*	Hydroxyurea*	Leflunomide*	Mycophenolate mofetil*	Thioguanine*	Tacrolimus*
Dosing	• Begin at 0.5 mg/kg, and monitor for cytopenia • If no cytopenia, increase dose by 0.5 mg/kg/d • After 6-8 wks increase by 0.5 mg/kg/d every 4 wks if necessary • The usual dose for psoriasis is 75-150 mg/d	• An initial dose of 500 mg twice daily, increasing to 3 g/day as tolerated. • A dose of 3-4.5 g/week has also been used.	• Loading dose of 100 mg/day for 3 days, followed by 20 mg/day	• 1.0-1.5 g orally two times/day	• Start at 80 mg two times/week; increase by 20 mg every 2-4 weeks • Maximum dose is 160 mg 3 times/week	• 0.05-0.15 mg/kg

Table 8. *Combination therapy for non-biologic systemic treatment of psoriasis*

	Acitretin	Apremilast	Cyclosporine	Fumaric acid esters	Methotrexate	Tofacitinib*
List of combination therapies	• Acitretin + PUVA • Acitretin + BB-UVB	• There is currently no substantial evidence to support the combined use of apremilast with other systemic or phototherapy treatments for psoriasis.			• Methotrexate + NB-UVB	• It can be used with methotrexate • Should not be combined with potent immuno-suppressants such as azathioprine and cyclosporine or with biologics • Not enough evidence to support the combined use of tofacitinib with other systemic agents or phototherapy