MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

POLICY	Transplant	**LAST REVIEW**	9/14/21
THERAPEUTIC CLASS	Immunosuppressive Agents	**REVIEW HISTORY** (MONTH/YEAR)	9/20, 9/19, 9/18, 5/17, 5/16
LOB AFFECTED	Medi-Cal		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

OVERVIEW

Organ transplant is a complex, high risk, and costly procedure. To minimize organ rejection, transplant patients usually take immunosuppressive therapy lifelong. However, these immunosuppressive agents carry their own risks, many related to increased risk of infections, metabolic syndrome, etc. The goal of immunosuppression therapy for organ transplant prevention is to minimize the side effects of immunosuppressants without compromising their efficacy. The below criteria, limits, and requirements for certain agents are in place to ensure appropriate use of those agents.

Transplant Rejection Prophylaxis Agents Formulary Positioning: *(Current as of 8/2021)*

Therapeutic Class	*Generic Name (Brand Name)*	*Available Strengths*	*Formulary Limits*	*Average Cost per 30 days*	*Notes*
Oral Immuno-suppressants	**Tacrolimus (Prograf)**	IR Capsules:			
		0.5 mg		$35.94	--
		1 mg		$110.39	--
		5 mg		$52.87	--
		IV solution:			
		5 mg/ml		--	--
	Tacrolimus (Astagraf XL Envarsus XR)	ER Capsule:			
		0.5 mg	**NF**	$126.81	Non-formulary. Formulary alternative = Tacrolimus IR capsules.
		1 mg		$697.44	
		5 mg		--	
		ER Tablet:			
		0.75 mg	**NF**	$155.00	Non-formulary. Formulary alternative = Tacrolimus IR capsules.
		1 mg		$355.02	
		4 mg		$744.95	
	Cyclosporine, modified (Gengraf, Neoral)	IR Capsules:			
		25 mg		$67.78	--
		50 mg		$47.51	
		100 mg		$145.96	
		Oral Solution:			
		100mg/ml		--	--
	Cyclosporine (Sandimmune)	Oral Solution:			
		100mg/ml	**--**	--	
		IR Capsules:			
		25 mg	**NF**	--	Non-formulary. Formulary alternative = cyclosporine (modified).
		50 mg		--	
		100 mg		$500.24	
		IV:			
		50 mg/ml	**NF**	--	
	Everolimus (Zortress)	Tablets:			
		0.25 mg	**PA, SP**	--	Approval is determined by medical necessity criteria. Restricted to specialty pharmacy.
		0.5 mg		$1,356.92	
		0.75 mg		$4,055.58	
		1 mg		--	

	Sirolimus (Rapamune)	IR Tablets:			
		0.5 mg	**PA, SP**	$56.77	Approval is determined by medical necessity criteria. Restricted to specialty pharmacy.
		1 mg		$369.28	
		2 mg		$536.40	
		Oral Solution			
		1 mg/ml	**PA, SP**	--	Approval is determined by medical necessity criteria. Restricted to specialty pharmacy.
	Azathioprine (Imuran, Azasan)	Tablets:			
		50 mg	**--**	$14.81	--
		Azasan 75 mg	**NF**	--	Non-formulary. Formulary alternative = Azathioprine
		Azasan 100 mg		--	
	Mycophenolate Mofetil (CellCept) Mycophenolate Acid (Myfortic DR)	IR Tablets:			
		250 mg	**--**	$33.03	--
		500 mg		$34.05	
		DR Tablets:			
		180 mg	**--**	$127.08	--
		360 mg		$148.33	
		Oral Suspension:			
		200 mg/ml	**--**	--	--
Injectable Agents	**Basiliximab (Simulect)**	IV Solution:			Approval is determined by medical necessity criteria and treatment failure to formulary agents.
		10 mg	**NF**	--	
		20 mg			
	Belatacept (Nulojix)	IV Solution:			
		250 mg	**NF**	$5,518.34	
	Alemtuzumab (Lemtrada)	IV Solution:			
		25 mg	**NF**	--	
	Antithymocyte Globulin (Thymoglobulin)	IV Solution:			
		25 mg	**NF**	--	

PA = Prior Authorization; NF = Non-Formulary; SP = Specialty Pharmacy; IR = Immediate Release; DR = Delayed Release

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ will make the determination based on Medical Necessity as described in HPSJ Medical Review Guidelines (UM06).

Oral Immunosuppressants

Tacrolimus (Prograf), Cyclosporine (Sandimmune), Cyclosporine modified (Gengraf, Neoral), Azathioprine (Imuran, Azasan), Mycophenolate Mofetil (CellCept), Mycophenolate Acid (Myfortic DR)

- ❒ **Coverage Criteria:** NONE
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** NONE
- ❒ **Non-Formulary:** Cyclosporine (Sandimmune), Tacrolimus (Astafraf XL, Envarsus XR), Azasan

Oral Immunosuppressants

Everolimus (Zortress), Sirolimus (Rapamune)

- ❒ **Coverage Criteria:** If medication is not being used for post-renal or post-liver transplant, approval is determined by medical necessity criteria. If used for post-renal or post-liver transplant, criteria is as follows:
  - Post-renal transplant

        - **Sirolimus** Reserved for concurrent treatment with cyclosporine or tacrolimus AND mycophenolate or azathioprine
        - **Everolimus** Reserved for concurrent treatment with cyclosporine or tacrolimus AND mycophenolate or azathioprine AND treatment failure/contraindication of sirolimus
    - Post-liver transplant
        - **Everolimus** Reserved for concurrent treatment with, or documented intolerance/contraindication of, cyclosporine or tacrolimus
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Documentation of past treatments tried, fill history, and if appropriate, justification for why cyclosporine, tacrolimus, mycophenolate or azathioprine is not appropriate.

Intravenous Immunosuppressant
Basiliximab (Simulect)

- ❒ **Non-formulary Coverage Criteria:** Approval is determined by medical necessity criteria.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Please submit clinic notes with documentation of acute organ rejection in patients receiving kidney or liver transplant.

Intravenous Immunosuppressant
Antithymocyte Globulin (Thymoglobulin)

- ❒ **Non-formulary Coverage Criteria:** Approval is determined by medical necessity criteria.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Please submit clinic notes with documentation of acute organ rejection in patients receiving kidney transplant.

Intravenous Immunosuppressant
Belatacept (Nulojix)

- ❒ **Coverage Criteria:** Approval is determined by medical necessity criteria.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Please submit clinic notes with documentation of kidney organ transplant in patients who are EBV seropositive.
- ❒ **Other:** To be used in combination with basiliximab induction, mycofenolate mofetil, and corticosteroids.

Intravenous Immunosuppressant
Alemtuzumab (Lemtrada)

- ❒ **Coverage Criteria:** Approval is determined by medical necessity criteria.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Approval is determined by medical necessity criteria. Please submit clinic notes with documentation of acute organ rejection in patients receiving kidney transplant where Basiliximab or Antithymocyte Globulin is inappropriate.
- ❒ **Notes:** Can cause significant lymphopenia that can lasts from 6 months to several years. Occasionally used off-label for kidney transplants.

Clinical Justification:

The goal of immunosuppression therapy for organ transplant prevention is to minimize the side effects of immunosuppressants without compromising their efficacy. Depending on the transplant type, a prophylaxis regimen can consist of monotherapy or a combination of agents. Immunosuppressive agents can be classified into 2 main categories: induction or maintenance.

Organ transplants with the highest risk for transplant rejection (e.g. heart, kidney, liver) may require induction therapy (i.e. Basiliximab, Thymoglobulin) to prevent acute organ rejection since the risk for organ rejection is highest within the first 6 months post-transplantation. Induction agents can also be used to delay the initial add-on of nephrotoxic calcineurin inhibitors (Cyclosporine, Tacrolimus).

Maintenance therapies are typically oral agents (cyclosporine, tacrolimus, sirolimus, mycophenolate, etc) and need to be taken lifelong. The dosing of these agents are titrated based on the serum concentration in the body—with target serum levels higher initially post-transplantation. It is generally not recommended to switch in between

agents once a patient is stable on a particular agent. The current trend is to use a combination of 3 maintenance therapies—usually a calcineurin-inhibitor (cyclosporine or tacrolimus), an antimetabolite agent (mycophenolate mofetil or azathioprine), and a glucocorticoid over the first year post-transplantation. Sirolimus and everolimus are Mammalian Target of Rapamycin (mTOR) inhibitors which are structurally similar to Tacrolimus but

considered to be a safer alternative for patients with renal insufficiency, although the use of everolimus within 3 months post-cardiac transplantation is not recommended due to a higher incidence of mortality from infections. Corticosteroids are used to lower the immune response. They are highly effective for the prevention and treatment of acute rejection, but their long-term use is associated with a number of adverse effects (i.e. worsening metabolic syndrome, fluid retention, osteoporosis, opportunistic infections, etc). Therefore, it is common to use corticosteroids in relatively high doses initially, then tapered to low doses or discontinued after 6 to 12 months post-transplantation. Patients with a history of one or more organ rejection may need to optimize drug therapies (switch from azathioprine to mycophenolate mofetil or switch from antimetabolite agents to an mTOR inhibitor).

Drug Utilization Review

Medi-Cal Utilization from September 2020 to August 2021						
	# Rx	Utilizers	Total Cost	Cost/Rx	Avg Qty	Cost/Unit
AZATHIOPRINE	**562**	**88**	**$8,320.94**	**$14.81**	**59.29**	**$0.25**
46771-AZATHIOPRINE 50 MG TABLET	562	88	$8,320.94	$14.81	59.29	$0.25
BELATACEPT	**1**	**1**	**$5,518.34**	**$5,518.34**	**3.00**	**$1,839.45**
30094-NULOJIX 250 MG VIAL	1	1	$5,518.34	$5,518.34	3.00	$1,839.45
CYCLOSPORINE	**10**	**1**	**$5,002.41**	**$500.24**	**60.00**	**$8.34**
13910-CYCLOSPORINE 100 MG CAPSULE	10	1	$5,002.41	$500.24	60.00	$8.34
CYCLOSPORINE, MODIFIED	**154**	**21**	**$18,875.12**	**$122.57**	**110.45**	**$1.11**
13916-CYCLOSPORINE MODIFIED 50 MG	20	3	$950.25	$47.51	55.50	$0.86
13918-CYCLOSPORINE MODIFIED 25 MG	75	12	$5,083.21	$67.78	125.20	$0.54
13918-NEORAL 25 MG GELATIN CAPSULE	7	1	$5,251.77	$750.25	325.71	$2.30
13919-CYCLOSPORINE MODIFIED 100 MG	52	11	$7,589.89	$145.96	81.35	$1.79
EVEROLIMUS	**47**	**4**	**$115,049.73**	**$2,447.87**	**116.17**	**$21.07**
24826-EVEROLIMUS 0.5 MG TABLET	28	3	$37,993.77	$1,356.92	83.57	$16.24
24827-EVEROLIMUS 0.75 MG TABLET	19	2	$77,055.96	$4,055.58	164.21	$24.70
MYCOPHENOLATE MOFETIL	**1786**	**211**	**$59,850.06**	**$33.51**	**134.73**	**$0.25**
47560-MYCOPHENOLATE 250 MG CAPSULE	942	108	$31,112.60	$33.03	165.35	$0.20
47561-MYCOPHENOLATE 500 MG TABLET	844	111	$28,737.46	$34.05	100.56	$0.34
MYCOPHENOLATE SODIUM	**391**	**43**	**$59,548.09**	**$152.30**	**116.10**	**$1.31**
19646-MYCOPHENOLIC ACID DR 180 MG TB	212	24	$26,941.95	$127.08	133.56	$0.95
19647-MYCOPHENOLIC ACID DR 360 MG TB	168	22	$24,919.12	$148.33	97.74	$1.52
19647-MYFORTIC 360 MG TABLET	11	1	$7,687.02	$698.82	60.00	$11.65
SIROLIMUS	**40**	**6**	**$11,856.69**	**$296.42**	**49.50**	**$5.99**
13696-SIROLIMUS 1 MG TABLET	23	3	$8,493.49	$369.28	54.78	$6.74
19299-SIROLIMUS 2 MG TABLET	5	1	$2,682.00	$536.40	30.00	$17.88
28502-SIROLIMUS 0.5 MG TABLET	12	2	$681.20	$56.77	47.50	$1.20
TACROLIMUS	**1970**	**188**	**$244,398.22**	**$124.06**	**127.51**	**$0.97**
28491-PROGRAF 1 MG CAPSULE	32	4	$22,318.02	$697.44	112.50	$6.20
28491-TACROLIMUS 1 MG CAPSULE (IMMED	1343	155	$148,256.83	$110.39	152.94	$0.72
28492-TACROLIMUS 5 MG CAPSULE (IMMED	44	5	$2,326.09	$52.87	67.95	$0.78
28495-PROGRAF 0.5 MG CAPSULE	18	2	$2,282.64	$126.81	40.83	$3.11
28495-TACROLIMUS 0.5 MG CAPSULE (IMM	385	47	$13,835.27	$35.94	80.95	$0.44
39120-ENVARSUS XR 0.75 MG TABLET	56	6	$8,680.19	$155.00	39.48	$3.93
39123-ENVARSUS XR 1 MG TABLET	56	8	$19,880.92	$355.02	69.52	$5.11
39124-ENVARSUS XR 4 MG TABLET	36	4	$26,818.26	$744.95	33.33	$22.35
Grand Total	**4961**	**386**	**$528,419.60**	**$106.51**	**120.05**	**$0.89**

There was an overall increase in total expenditure (approximately $36,000 increase) for transplant medications from September 2020 to August 2021 compared to the prior year. The main contributing factor to the total spend was due to the use of tacrolimus, at 46% of the total spend with the main dose/formulation used as tacrolimus 1 mg immediate release capsules (82% of the tacrolimus utilization, 68.17% of the tacrolimus fills). Tacrolimus was also the most highly utilized immunosuppressant medication at 40% of the overall fills and 48.7% of the overall utilizers. The next highest cost medication used was everolimus (approximately 22% of the overall spend) by 4 patients with only 0.1% of the total overall fills. The next highly utilized agent was mycophenolate mofetil at 36% of the overall fills, 55% of the overall utilizers, but only 11.2% of the overall spend. It is, however, important to note that the initial coverage of transplant medications are covered by fee-for-service (FFS) and the patients are disenrolled to be re-enrolled into FFS for this coverage to avoid any barriers to their post-transplant care. After a certain amount of time, the patients have the option of re-enrolling back into HPSJ where they continue their immunosuppression regimen. Note that some of these medications are not specific for transplant (i.e. cyclosporine for autoimmune disorders), which may cause an increase in utilization for these types of medications. Overall, the utilization summary is in alignment with the national guideline recommendations for first-line transplant prophylaxis agents as well as HPSJ formulary.

Newly Approved Medications not on Formulary

N/A

Guideline & Literature Review

In regards to post-renal transplant patients, KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients recommend a combination of immunosuppressive medications as maintenance therapy, including a calcineurin inhibitor (i.e. cyclosporine or tacrolimus) and an antiproliferative agent (i.e. mycophenolate or azathioprine). For post-liver transplant patients, calcineurin inhibitors are typically reserved as a first-line therapy. mTOR inhibitors (i.e. Zortress and sirolimus) is typically reserved as add-on therapy to a patient's current regimen, or if a patient cannot tolerate, or has a contraindication to, a calcineurin inhibitor.

Criteria Review for Unnecessary Barriers

Current requirements are appropriate

Recommendations

Perform review on an annual basis.

References

1. Lucey M, Terrault N, Ojo L, et al. Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. AASLD/AST. 2012: DOI: 10.1002/lt.23566.
2. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009). Kidney Disease Improving Global Outcomes. 2009; 9(30).
3. 2008 guideline on clinical investigation of immunosuppressants for solid organ transplantation. Committee for Medicinal Products for Human Sse (CHMP)/ European Medicines Agency (EMA). 2008. London, UK: Ref # 263148/06.
4. Faro A, Mallory GB, Visner GA, et al. American Society of Transplantation Executive Summary on Pediatric Lung Transplantation. American Journal of Transplantation. 2006; 7(2): 285-292.
5. Moini M., Schilsky M., and Tichy E. Review on immunosuppression in liver transplantation: World Journal of Hepatology. Journal List World J Hepatol v.7(10); 2015 Jun 8 PMC4450199

Review & Edit History

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	HPSJ Coverage Policy – Immunology – Transplant 2016-05.docx	5/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Immunology – Transplant 2017-05.docx	5/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Immunology – Transplant 2018-09.docx	9/2018	Johnathan Yeh, PharmD

Update to Policy	HPSJ Coverage Policy – Immunology – Transplant 2019-09.docx	9/2019	Matthew Garrett, PharmD
Update to Policy	HPSJ Coverage Policy – Immunology – Transplant 2020-09.docx	9/2020	Matthew Garrett, PharmD
Review of Policy	Transplant.docx	9/2021	Matthew Garrett, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy