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Abatacept

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Related Policies (if applicable)
RX502.061: Oncology Medications

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: This medical policy does NOT address oncologic indications. This medical policy IS NOT TO BE USED for oncologic indications. Refer to RX502.061 Oncology Medications for oncologic indications.

Abatacept (Orencia®) may be self-administered. Refer to the applicable pharmacy benefit plan when self-administered.

Abatacept (Orencia®) **may be considered medically necessary** when administered intravenously (IV) for the following indications:

- Moderately to severely active rheumatoid arthritis (RA) in adults (**NOTE 2**) if there is a previous failure of:
    1. One or more conventional disease-modifying antirheumatic drug(s) (DMARDs) (hydroxychloroquine, sulfasalazine, leflunomide, methotrexate), OR
    2. A previous biological DMARD;
- Active psoriatic arthritis (PsA) in adults;
- Moderately to severely active polyarticular juvenile idiopathic arthritis in individuals 6 years of age or older (**NOTE 3**) if there is a previous failure of:
    1. One or more conventional disease-modifying antirheumatic drug(s) (DMARDs) (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), OR
    2. A previous biological DMARD;
- Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric individuals 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor;
- Chronic graft-versus-host disease (cGVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

NOTE 2: Orencia may be used as monotherapy or concomitantly with DMARDs other than tumor necrosing factor (TNF) antagonists.

NOTE 3: Orencia may be used as monotherapy or concomitantly with methotrexate.

The use of Orencia for all other indications **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Orencia, a selective costimulation modulator, inhibits T-cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a co-stimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) and are found in the synovium of patients with RA and PsA.

Rheumatoid Arthritis
Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease in which the immune system attacks healthy cells by mistake, causing inflammation or painful swelling in affected parts of the body. RA mainly attacks the joints in the hands, wrists and knees, and usually attacks many joints at the same time. The lining of the joint becomes inflamed, causing damage to joint tissue, which in turn causes long-lasting or chronic pain, unsteadiness and deformity of the affected joints. RA can also affect other tissues in the body and cause problems in organs such as the lungs, heart and eyes. (3)

Psoriatic Arthritis
Psoriatic arthritis (PsA) is a condition involving joint inflammation (arthritis) that usually occurs in conjunction with psoriasis, a skin disorder characterized by patches of red, irritated skin that are often covered by flaky white scales. Psoriasis may cause changes to fingernails and toenails, causing pitting, ridges, crumbling of the nail or separation of the nail from the nail bed. PsA causes stiff, painful joints with redness, heat and swelling in the surrounding tissues. Swelling and redness may result in a sausage-like appearance of the fingers or toes when the hands or feet are affected. Psoriasis appears before joint problems develop in most people. It typically begins during adolescence or as a young adult, with PsA occurring between the ages of 30 and 50. Both conditions may occur at any age; and in a small number of cases, PsA develops without any noticeable skin changes. (4)

Polyarticular Juvenile Idiopathic Arthritis
Polyarticular juvenile idiopathic arthritis (formerly called polyarticular-onset juvenile rheumatoid arthritis [JRA]) is a subset of juvenile idiopathic arthritis (JIA) that is defined by the presence of more than four affected joints during the first six months of illness. This disease, which comprises 20 to 30 percent of patients with JIA, is included in the group termed "childhood polyarthritis." Polyarticular JIA is more frequent in females than males. There is a bimodal distribution of the age at onset. The first peak is between the ages of two and five years, and the second is between 10 and 14 years. This age distribution suggests that two or more distinct diseases may be included in this classification. In children less than 10 years of age, polyarticular JIA often begins similarly to oligoarticular disease, with one or two joints

affected. The development of the disease is often indolent until an intercurrent infection precipitates a dramatic increase in symptoms. The disease then becomes relentlessly progressive, spreading to involve five or more joints within the first six months after disease onset. Joint involvement is symmetric, with the knees, wrists, and ankles most frequently affected. There are typically periods of apparent response to therapy followed by relapses with an increasing number of involved joints. Polyarticular JIA may go unrecognized at first because of its initial indolent course. This failure to recognize the initial symptoms may make it appear that the disease had a sudden onset and rapid progression. In older children and adolescents, these patients usually have a relatively rapid onset of inflammation in multiple joints, including involvement of the many small joints of the hands and feet, within two to three months of disease onset. Pain in the small joints is a common manifestation of polyarticular JIA and initially may be out of proportion to the degree of inflammation and stiffness. The joints of the fingers, wrists, elbows, hips, knees, and ankles are most commonly affected. (2)

Graft Versus Host Disease (GVHD)

The development of acute and/or chronic GVHD is a major complication of allogeneic hematopoietic cell transplantation (HCT) and is associated with significant morbidities and non-relapse mortality (NRM) in allogeneic HCT recipients. Increasing incidence of GVHD has been observed in recent years, primarily due to the increased use of unrelated and/or human leukocyte antigen (HLA)-mismatched donors and granulocyte-colony stimulating factor (G-CSF)–mobilized peripheral blood progenitor cells (PBPCs), among other factors. Mild manifestations limited to a single organ are often managed with close observation, with topical treatment, or by slowing the tapering of immunosuppressive agents. More severe manifestations or multi-organ involvement typically require systemic corticosteroid treatment (with or without secondary systemic agents). Management of GVHD can be optimized by providing coordinated care from a multidisciplinary team, preferably in medical centers with access to specialized transplant services. (7)

Regulatory Status

Orencia® (abatacept) was approved by the U.S. Food and Drug Administration (FDA) in 2005 for intravenous use in the treatment of RA. In 2011, the FDA approved a subcutaneous formulation for adults with moderate to severe rheumatoid arthritis; and in 2017, it was approved for treatment of active PsA in adults. In December 2021, the FDA approved Orencia for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor. (5) In October 2023, the FDA approved an expansion of Orencia subcutaneous use to include treatment of patients aged 2 years and older with active psoriatic arthritis (PsA). (1)

Rationale

This policy was originally developed in 2020 and is based on the U.S. Food and Drug Administration (FDA) labeled indications and guidance from the National Comprehensive Cancer Network (NCCN) through August 2024.

Rheumatoid Arthritis (RA) (1)

The efficacy and safety of Orencia® (abatacept) for intravenous administration were assessed in six randomized, double-blind, controlled studies (five placebo-controlled and one active controlled) in patients ≥18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Studies I, II, III, IV, and VI required patients to have at least 12 tender and 10 swollen joints at randomization. Study V did not require any specific number of tender or swollen joints. Orencia or placebo treatment was given intravenously at weeks 0, 2, and 4 and then every 4 weeks thereafter in intravenous Studies I, II, III, IV, and VI. The safety and efficacy of Orencia for subcutaneous administration were assessed in Study SC-1, which was a randomized, double-blind, double-dummy, non-inferiority study that compared abatacept administered subcutaneously and intravenously in 1457 subjects with rheumatoid arthritis (RA), receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate (MTX-IR).

Study I evaluated Orencia as monotherapy in 122 patients with active RA who had failed at least one non-biologic disease modifying antirheumatic drug (DMARD) or etanercept. In Study II and Study III, the efficacy of Orencia were assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX. In Study IV, the efficacy of Orencia was assessed in patients with an inadequate response to a tumor necrosing factor (TNF) antagonist, with the TNF antagonist discontinued prior to randomization; other DMARDs were permitted. Study V primarily assessed safety in patients with active RA requiring additional intervention in spite of current therapy with DMARDs; all DMARDs used at enrollment were continued. Patients in Study V were not excluded for comorbid medical conditions. In Study VI, the efficacy and safety of Orencia were assessed in MTX-naive patients with RA of less than 2 years disease duration. In Study VI, patients previously naive to MTX were randomized to receive Orencia plus MTX or MTX plus placebo. In Study SC-1, the goal was to demonstrate the efficacy and safety of Orencia subcutaneous relative to Orencia intravenous administration in subjects with moderate to severely active RA and experiencing inadequate response to MTX, using a non-inferiority study design.

Study I patients were randomized to receive one of three doses of Orencia (0.5, 2, or 10 mg/kg) or placebo ending at week 8. Study II patients were randomized to receive Orencia 2 or 10 mg/kg or placebo for 12 months. Study III, IV, V, and VI patients were randomized to receive a dose of Orencia based on weight range or placebo for 12 months (Studies III, V, and VI) or 6 months (Study IV). The dose of Orencia was 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1,000 mg for patients weighing greater than 100 kg. In Study SC-1, patients were randomized with stratification by body weight (<60 kg, 60 to 100 kg, >100 kg) to receive Orencia 125 mg subcutaneous injections weekly, after a single intravenous loading dose of Orencia based on body weight or Orencia intravenously on Days 1,

15, 29, and every four weeks thereafter. Subjects continued taking their current dose of MTX from the day of randomization.

Clinical Response

The percent of Orencia-treated patients achieving ACR 20, 50, and 70 responses and major clinical response in Studies I, III, IV, and VI are shown in Table 1. Orencia-treated patients had higher ACR 20, 50, and 70 response rates at 6 months compared to placebo-treated patients. Month 6 ACR response rates in Study II for the 10 mg/kg group were similar to the Orencia group in Study III.

In Studies III and IV, improvement in the ACR 20 response rate versus placebo was observed within 15 days in some patients and within 29 days versus MTX in Study VI. In Studies II, III, and VI, ACR response rates were maintained to 12 months in Orencia-treated patients. ACR responses were maintained up to three years in the open-label extension of Study II. In Study III, Orencia-treated patients experienced greater improvement than placebo-treated patients in morning stiffness.

In Study VI, a greater proportion of patients treated with Orencia plus MTX achieved a low level of disease activity as measured by a disease activity score 28 with C-reactive protein (DAS28-CRP) less than 2.6 at 12 months compared to those treated with MTX plus placebo (Table 1). Of patients treated with Orencia plus MTX who achieved DAS28-CRP less than 2.6, 54% had no active joints, 17% had one active joint, 7% had two active joints, and 22% had three or more active joints, where an active joint was a joint that was rated as tender or swollen or both.

In Study SC-1, the main outcome measure was ACR 20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of −7.5%. As shown in Table 2, the study demonstrated non-inferiority of Orencia administered subcutaneously to intravenous infusions of Orencia with respect to ACR 20 responses up to 6 months of treatment. ACR 50 and 70 responses are also shown in Table 1. No major differences in ACR responses were observed between intravenous and subcutaneous treatment groups in subgroups based on weight categories (less than 60 kg, 60 to 100 kg, and more than 100 kg; data not shown).

Table 1. Clinical Response in Controlled Trials

	Percent of Patients				
	Intravenous Administration				**Subcutaneous or Intravenous Administration**
	Inadequate Response to DMARDs	**Inadequate Response to Methotrexate (MTX)**	**Inadequate Response to TNF Antagonists**	**MTX-Naïve**	**Inadequate Response to MTX**
	Study I	**Study III**	**Study IV**	**Study VI**	**Study SC-1**

Response Rate	ORN [a] n = 32	PBO[b] n= 32	ORN[b] +MTX n= 424	PBO +MTX n= 214	ORN[b] + DMARDs n=256	PBO + DMARDs n=133	ORN[b] + MTX n= 256	PBO + MTX n= 253	ORN[e] SC + MTX n= 693	ORN[e] IV + MTX n= 678
ACR 20										
Month 3	53%	31%	62%[h]	37%	46%[h]	18%	64%[f]	53%	68%	69%
Month 6	NA	NA	68%[h]	40%	50%[h]	20%	75%[g]	62%	76%[i]	76%
Month 12	NA	NA	73%[h]	40%	NA	NA	76%[h]	62%	NA	NA
ACR 50										
Month 3	16%	6%	32%[h]	8%	18%[g]	6%	40%[h]	23%	33%	39%
Month 6	NA	NA	40%[h]	17%	20%[h]	4%	53%[h]	38%	52%	50%
Month 12	NA	NA	48%[h]	18%	NA	NA	57%[h]	42%	NA	NA
ACR70										
Month 3	6%	0	13%[h]	3%	6%[f]	1%	19%[g]	10%	13%	16%
Month 6	NA	NA	20%[h]	7%	10%[g]	2%	32%[g]	20%	26%	25%
Month 12	NA	NA	29%[h]	6%	NA	NA	43%[h]	27%	NA	NA
Major Clinical Response[c]	NA	NA	14%[h]	2%	NA	NA	27%[h]	12%	NA	NA
DAS28-CRP <2.6[d]										
Month 12	NA	NA	NA	NA	NA	NA	41%[h]	23%	NA	NA

ORN: Orencia
PBO: placebo
TNF: tumor necrosing factor
DMARDs: disease modifying antirheumatic drugs
SC: subcutaneous
IV: intravenous
DAS28-CRP: disease activity score 28 with C-reactive protein
[a] 10 mg/kg.
[b] Dosing based on weight range.
[c] Major clinical response is defined as achieving an ACR 70 response for a continuous 6-month period.
[d] Refer to text for additional description of remaining joint activity.
[e] Per protocol data is presented in table. For ITT; n=736, 721 for SC and IV ORENCIA, respectively.
[f] p<0.05, ORENCIA (ORN) vs placebo (PBO) or MTX.
[g] p<0.01, ORENCIA vs placebo or MTX.
[h] p<0.001, ORENCIA vs placebo or MTX.
[i] 95% CI: −4.2, 4.8 (based on prespecified margin for non-inferiority of −7.5%).

The results of the components of the ACR response criteria for Studies III, IV, and SC-1 are shown in Table 2 (results at Baseline [BL] and 6 months [6 M]). In Orencia-treated patients, greater improvement was seen in all ACR response criteria components through 6 and 12 months than in placebo-treated patients.

Table 2. Components of ACR Responses at 6 Months

	Intravenous Administration								**Subcutaneous (SC) or Intravenous (IV) Administration**			
	Inadequate Response to Methotrexate (MTX)				**Inadequate Response to TNF Antagonists**				**Inadequate Response to MTX**			
	Study III				**Study IV**				**Study SC-1[c]**			
	ORN + MTX n = 424		**PBO + MTX n = 214**		**ORN + DMARDs n = 256**		**PBO + DMARDs n = 133**		**ORN SC + MTX n = 693**		**ORN IV + MTX n = 678**	
Component (median)	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M	BL	6 M
Number of tender joints (0-68)	28	7[e]	31	14	30	13[e]	31	24	27	5	27	6
Number of swollen joints (0-66)	19	5[e]	20	11	21	10[e]	20	14	18	4	18	3
Pain[a]	67	27[e]	70	50	73	43[d]	74	64	71	25	70	28
Patient global assessment[a]	66	29[e]	64	48	71	44[e]	73	63	70	26	68	27
Disability index[b]	1.75	1.13[e]	1.75	1.38	1.88	1.38[e]	2.00	1.75	1.88	1.00	1.75	1.00
Physician global assessment[a]	69	21[e]	68	40	71	32[e]	69	54	65	16	65	15
CRP (mg/dL)	2.2	0.9[e]	2.1	1.8	3.4	1.3[e]	2.8	2.3	1.6	0.7	1.8	0.7

TNF: tumor necrosis factor
CRP: C-reactive protein
[a] Visual analog scale: 0 = best, 100 = worst.
[b] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[c] SC-1 is a non-inferiority study. Per protocol data is presented in table.
[d] $p<0.01$, ORENCIA (ORN) vs placebo (PBO), based on mean percent change from baseline.
[e] $p<0.001$, ORENCIA vs placebo, based on mean percent change from baseline.

The percent of patients achieving the ACR 50 response for Study SC-1 in the Orencia subcutaneous (SC) and intravenous (IV) treatment arms at each treatment visit was as follows: Day 15—SC 3%, IV 5%; Day 29—SC 11%, IV 14%; Day 57—SC 24%, IV 30%; Day 85—SC 33%, IV 38%; Day 113—SC 39%, IV 41%; Day 141—SC 46%, IV 47%; Day 169—SC 51%, IV 50%.

Radiographic Response

In Study III and Study VI, structural joint damage was assessed radiographically and expressed as change from baseline in the Genant-modified Total Sharp Score (TSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score. Orencia/MTX slowed the progression of structural damage compared to placebo/MTX after 12 months of treatment as shown in Table 3.

Table 3. Mean Radiographic Changes in Study III[a] and Study VI[b]

Parameter	Orencia/MTX	Placebo/MTX	Differences	P-value[d]
Study III				
First Year				
TSS	1.07	2.43	1.36	<0.01
ES	0.61	1.47	0.86	<0.01
JSN score	0.46	0.97	0.51	<0.01
Study III				
Second Year				
TSS	0.48	0.74[c]	-	-
ES	0.23	0.22[c]	-	-
JSN score	0.25	0.51[c]	-	-
Study VI				
First Year				
TSS	0.6	1.1	0.5	0.04

MTX: methotrexate
TSS: total sharp score
ES: erosion score
JSN: joint narrowing score
[a] Patients with an inadequate response to MTX.
[b] MTX-naive patients.
[c] Patients received 1 year of placebo/MTX followed by 1 year of Orencia/MTX.
[d] Based on a nonparametric ANCOVA model.

In the open-label extension of Study III, 75% of patients initially randomized to Orencia/MTX and 65% of patients initially randomized to placebo/MTX were evaluated radiographically at Year 2. As shown in Table 3, progression of structural damage in Orencia/MTX-treated patients was further reduced in the second year of treatment.

Following 2 years of treatment with Orencia/MTX, 51% of patients had no progression of structural damage as defined by a change in the TSS of zero or less compared with baseline. Fifty-six percent (56%) of Orencia/MTX-treated patients had no progression during the first year compared to 45% of placebo/MTX-treated patients. In their second year of treatment with Orencia/MTX, more patients had no progression than in the first year (65% vs 56%).

Physical Function Response and Health-Related Outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, Orencia demonstrated greater improvement from

baseline versus placebo in Studies II-V and versus MTX in Study VI. In Study SC-1, improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous Orencia administration. The results from Studies II and III are shown in Table 4. Similar results were observed in Study V compared to placebo and in Study VI compared to MTX. During the open-label period of Study II, the improvement in physical function has been maintained for up to 3 years.

Table 4. Mean Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)

	Inadequate Response to Methotrexate (MTX)			
	Study II		**Study III**	
HAQ Disability Index	**Orencia[a] + MTX (n = 115)**	**Placebo + MTX (n = 119)**	**Orencia[b] + MTX (n = 422)**	**Placebo + MTX (n = 212)**
Baseline (Mean)	0.98[c]	0.97[c]	1.69[d]	1.69[d]
Mean Improvement Year 1	0.40[c,e]	0.15[c]	0.66[d,e]	0.37[d]

[a] 10 mg/kg.
[b] Dosing based on weight range.
[c] Modified Health Assessment Questionnaire: 0 = best, 3 = worst; 8 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[d] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[e] $p<0.001$, Orencia vs placebo.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in Studies II, III, and IV and at 12 months in Studies II and III. In these studies, improvement was observed in the Orencia group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Adult Psoriatic Arthritis (PsA)

The efficacy of Orencia was assessed in 594 patients with psoriatic arthritis (PsA), in two randomized, double-blind, placebo-controlled studies (Studies PsA-I and PsA-II) in adult patients, age 18 years and older. Patients had active PsA (≥3 swollen joints and ≥3 tender joints) despite prior treatment with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter. In PsA-I and PsA-II, 37% and 61% of patients, respectively, were treated with tumor necrosis factor antagonists previously.

In PsA-I, a dose-ranging study, 170 patients received study drug IV at Day 1, 15, 29, and then every 28 days thereafter in a double-blind manner for 24 weeks, followed by open-label Orencia every 28 days. Patients were randomized to receive placebo or Orencia 3 mg/kg, 10 mg/kg (weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1,000 mg for patients weighing greater than 100 kg), or two doses of 30 mg/kg followed by weight range-based dosing of 10 mg/kg without escape for 24

weeks. Patients were allowed to receive stable doses of concomitant MTX, low dose corticosteroids (equivalent to ≤10 mg of prednisone) and/or NSAIDs during the trial. At enrollment, approximately 60% of patients were receiving MTX. At baseline, the mean (SD) CRP for Orencia IV was 17 mg/L (33.0) and mean number (SD) of tender joints and swollen joints was 22.2 (14.3) and 10.9 (7.6), respectively.

In PsA-II, 424 patients were randomized 1:1 to receive weekly doses of SC placebo or Orencia 125 mg without a loading dose for 24 weeks-in a double-blind manner, followed by open-label Orencia 125 mg SC weekly. Patients were allowed to receive stable doses of concomitant MTX, sulfasalazine, leflunomide, hydroxychloroquine, low dose corticosteroids (equivalent to ≤10 mg of prednisone) and/or NSAIDs during the trial. At randomization, 60% of patients were receiving MTX. The baseline disease characteristics included presence of joint erosion on X-rays in 84% (341/407) with a mean (SD) PsA-modified Sharp van der Heijde erosion score (SHS) of 10.8 (24.2), elevated serum C reactive protein (CRP) in 66% (277/421) with a mean (SD) of 14.1 mg/L (25.9), and polyarticular disease in 98% (416/424) of patients with a mean number (SD) of tender joints and swollen joints of 20.2 (13.3) and 11.6 (7.5), respectively. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by Week 16 escaped to open-label SC Orencia 125 mg weekly.

The primary endpoint for both PsA-I and PsA-II was the proportion of patients achieving ACR 20 response at Week 24 (Day 169).

Clinical Response

A greater proportion of adult patients with PsA achieved an ACR20 response after treatment with Orencia 10 mg/kg IV (weight range-based dosing as described above) or 125 mg SC compared to placebo at Week 24. Responses were seen regardless of prior TNF antagonist treatment and regardless of concomitant non-biologic DMARD treatment. The percent of patients achieving ACR 20, 50, or 70 responses in Studies PsA-I and PsA-II are presented in Table 5 below.

Table 5. Proportion of Patients with ACR Responses at Week 24 in Studies PsA-I and PsA-II[a]

	PsA-I		**PsA-II**	
	Orencia 10 mg/kg Intravenous[b] N = 40	**Placebo N =42**	**Orencia 125 mg Subcutaneous N = 213**	**Placebo N = 211**
ACR 20	47.5%[c]	19.0%	39.4%[c]	22.3%
ACR 50	25.0%	2.4%	19.2%	12.3%
ACR 70	12.5%	0%	10.3%	6.6%

[a] Patients who had less than 20% improvement in tender or swollen joint counts at Week 16 met escape criteria and were considered non-responders.

[b] Weight range-based dosing.

[c] $p<0.05$ versus placebo.

Results were generally consistent across the ACR components in Study PsA-I and PsA-II.

Improvements in enthesitis and dactylitis were seen with Orencia treatment at Week 24 in both PsA-I and PsA-II.

Physical Function Response

In study PsA-I, there was a higher proportion of patients with at least a 0.30 decrease from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24, with an estimated difference for Orencia 10 mg/kg (weight range-based dosing) (45%) vs. placebo (19%) of 26.1 (95% confidence interval [CI]: 6.8, 45.5). In study PsA-II, the proportion of patients with at least a 0.35 decrease from baseline in HAQ-DI on Orencia was 31%, as compared to 24% on placebo (estimated difference: 7%; 95% CI: -1%, 16%). There was a higher adjusted mean change from baseline in HAQ-DI on Orencia (-0.33) vs. placebo (-0.20) at Week 24, with an estimated difference of -0.13 (95% CI: -0.25, -0.01).

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Intravenous Administration

The safety and efficacy of Orencia with intravenous administration were assessed in Study JIA-1, a three-part study including an open-label extension in pediatric patients with pJIA. Patients 6 to 17 years of age (n=190) with moderately to severely active pJIA who had an inadequate response to one or more DMARDs, such as MTX or TNF antagonists, were treated. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean, 16) and joints with loss of motion (mean, 16); patients had elevated C-reactive protein (CRP) levels (mean, 3.2 mg/dL) and ESR (mean, 32 mm/h). The patients enrolled had subtypes of JIA that at disease onset included oligoarticular (16%), polyarticular (64%; 20% were rheumatoid factor positive), and systemic JIA without systematic manifestations (20%). At study entry, 74% of patients were receiving MTX (mean dose, 13.2 mg/m2 per week) and remained on a stable dose of MTX (those not receiving MTX did not initiate MTX treatment during the study).

In Period A (open-label, lead-in), patients received 10 mg/kg (maximum 1,000 mg per dose) intravenously on days 1, 15, 29, and monthly thereafter. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Patients demonstrating an ACR Pedi 30 response at the end of Period A were randomized into the double-blind phase (Period B) and received either Orencia or placebo for 6 months or until disease flare. Disease flare was defined as a ≥30% worsening in at least 3 of the 6 JIA core set variables with ≥30% improvement in not more than 1 of the 6 JIA core set variables; ≥2 cm of worsening of the Physician or Parent Global Assessment was necessary if used as 1 of the 3 JIA core set variables used to define flare, and worsening in ≥2 joints was necessary if the number of active joints or joints with limitation of motion was used as 1 of the 3 JIA core set variables used to define flare.

At the conclusion of Period A, pediatric ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. Pediatric ACR 30 responses were similar in all subtypes of JIA studied.

During the double-blind randomized withdrawal phase (Period B), Orencia-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53%); 95% CI of the difference (15%, 52%). The risk of disease flare among patients continuing on intravenous Orencia was less than one-third than that for patients withdrawn from Orencia treatment (hazard ratio=0.31, 95% CI [0.16, 0.59]). Among patients who received intravenous Orencia throughout the study (Period A, Period B, and the open-label extension Period C), the proportion of pediatric ACR 30/50/70 responders has remained consistent for 1 year.

Subcutaneous Administration

Orencia for subcutaneous administration without an intravenous loading dose was assessed in Study JIA-2, a 2-period, open-label study that included pediatric patients 2 to 17 years of age (n=205). Patients had active polyarticular disease at the time of the study and had inadequate response to at least one nonbiologic or biologic DMARD. The JIA patient subtypes at study entry included polyarticular (79%; 22% were rheumatoid factor positive), extended and persistent oligoarticular (14%), enthesitis-related arthritis (1%), and systemic JIA without systemic manifestations (2%). Patients had a mean disease duration of 2.5 years with active joints (mean, 11.9), joints with loss of motion (mean, 10.4), and elevated C-reactive protein (CRP) levels (mean, 1.2 mg/dL). At study entry, 80% of patients were receiving MTX and remained on a stable dose of MTX. Patients received weekly open-label Orencia subcutaneously by a weight-tiered dosing regimen. The primary objective of the study was evaluation of pharmokinetic (PK) in order to support the extrapolation of efficacy based on exposure to Orencia supported by descriptive efficacy.

JIA ACR 30/50/70 responses assessed at 4 months in the 2- to 17-year-old patients were consistent with the results from the intravenous study, JIA-1.

Prophylaxis of Acute Graft versus Host Disease (aGVHD) (1)

The efficacy of Orencia, in combination with a calcineurin inhibitor (CNI) and methotrexate (MTX), for the prophylaxis of acute graft versus host disease (aGVHD), was based on a multicenter, two cohort clinical study (GVHD-1, NCT01743131) in patients age 6 years and older who underwent hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor (URD). The two cohorts in GVHD-1 included:

1) An open-label, single-arm study of 43 patients who underwent a 7 of 8 Human Leukocyte Antigen (HLA)-matched HSCT (7 of 8 cohort); and
2) A randomized (1:1), double-blind, placebo-controlled study of patients who underwent an 8 of 8 HLA-matched HSCT who received Orencia or placebo in combination with a CNI and MTX (8 of 8 cohort).

In both the 7/8 and 8/8 cohorts, Orencia was administered at a dose of 10 mg/kg (1,000 mg maximum dose) as an intravenous infusion over 60 minutes, beginning on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation.

Baseline demographic and clinical characteristics of both the 7 of 8 and 8 of 8 cohorts are outlined below in Table 6.

Table 6. Baseline Demographic and Clinical Characteristics: 7 of 8 and 8 of 8 Cohort Treated Analysis Population in Study GVHD-1

	7 of 8 Cohort	**8 of 8 Cohort**	
	ORENCIA (+CNI and MTX) N=43	**ORENCIA (+CNI and MTX) N=73**	**Placebo (+CNI and MTX) N=69**
Age – Median	38	44	40
Age – Range	6-76	6-71	7-74
Gender - Male	27 (63)	41 (56)	37 (54)
White	31 (72)	63 (86)	61 (88)
Black or African American	7 (16)	3 (4.1)	2 (2.9)
Asian	2 (4.7)	4 (6)	2 (2.9)
Hispanic	7 (16)	4 (6)	2 (2.9)
Malignancy type			
Acute Myeloid Leukemia (AML)	15 (35)	30 (41)	22 (32)
Myelodysplastic Syndrome (MDS)	11 (26)	15 (21)	12 (17)
Acute Lymphoblastic Leukemia (ALL)	8 (19)	20 (27)	22 (32)
Acute leukemia or ambiguous lineage	1 (2.3)	0	1 (1.4)
Hodgkin and Non-Hodgkin lymphoma	1 (2.3)	1 (1.4)	1 (1.4)
Acute Lymphoblastic Lymphoma in 2nd or Greater Complete Remission	1 (2.3)	4 (6)	1 (1.4)
Chronic Myelomonocytic leukemia	1 (2.3)	1 (1.4)	4 (6)
Chronic Myelogenous leukemia	4 (9)	1 (1.4)	5 (7)
Not reported	1 (2.3)	1 (1.4)	1 (1.4)
GVHD Prophylaxis			
Cyclosporine	16 (37)	11 (15)	11 (16)
Tacrolimus	27 (63)	62 (85)	58 (84)
Type of Graft			
Bone Marrow	21 (49)	33 (45)	26 (38)
Cytokine Mobilized Peripheral Blood (PBSC)	22 (51)	40 (55)	43 (62)

Conditioning Regimen			
TBI and Chemotherapy	11 (26)	20 (27)	26 (38)
Busulfan and Cyclophosphamide	13 (30)	28 (38)	21 (30)
Busulfan and Fludarabine	8 (19)	7 (10)	2 (2.9)
Melphalan and Fludarabine	11 (26)	18 (25)	20 (29)

CNI: calcineurin inhibitor
MTX: methotrexate

Efficacy was established based on overall survival (OS) and grade II-IV aGVHD free survival (GFS) results assessed at Day 180 post-transplantation. Orencia + CNI and MTX did not significantly improve grade III-IV GFS versus placebo + CNI and MTX at Day 180 post-transplantation. The efficacy results of the GVHD-1 8 of 8 cohort are shown in Table 7.

Table 7. Efficacy Results in 8 of 8 Cohort in Study GVHD-1 at Day 180 Post-Transplantation

Endpoint	**ORENCIA (+CNI and MTX) n=73**	**Placebo (+CNI and MTX) n=69**
Gr III-IV aGVHD Free Survival[a] Rate (95% CI)	87% (77%, 93%)	75% (63%, 84%)
Hazard Ratio (95% CI)	0.55 (0.26, 1.18)	
Gr II-IV aGVHD Free Survival[b] Rate (95% CI)	50% (38%, 61%)	32% (21%, 43%)
Hazard Ratio (95% CI)	0.54 (0.35, 0.83)	
Overall Survival Rate (95% CI)	97% (89%, 99%)	84% (73%, 91%)
Hazard Ratio (95% CI)	0.33 (0.12, 0.93)	

CNI: calcineurin inhibitor
MTX: methotrexate
CI: confidence interval
aGVHD: Acute Graft versus Host Disease
[a] Gr III-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade III-IV aGVHD, or death by any cause up to Day 180 post-transplantation.
[b] Gr II-IV aGVHD Free Survival was measured from the date of transplantation until the onset of documented Grade II-IV aGVHD, or death by any cause up to Day 180 post-transplantation.

In an exploratory analysis of the 7 of 8 cohort of Orencia-treated patients (n=43), the rates of Grade III-IV GVHD-free survival, Grade II-IV GVHD-free survival, and OS at day 180 post-transplantation were 95% (95% CI 83%, 99%), 53% (95% CI 38%, 67%), and 98% (95% CI 85%, 100%), respectively.

Graft versus host disease (GVHD)-2 was a clinical study that used data from the Center for International Blood and Marrow Transplant Research (CIBMTR). The study analyzed outcomes of Orencia in combination with a CNI and MTX, versus a CNI and MTX alone, for the prophylaxis

of aGVHD, in patients 6 years of age or older who underwent HSCT from a 1 allele-mismatched URD between 2011 and 2018. The Orencia + CNI and MTX-treated group (n=54) included 42 patients from GVHD-1, in addition to 12 patients treated with Orencia outside of GVHD-1. The comparator group (n=162) was randomly selected in a 3:1 ratio to the Orencia-treated group from the CIBMTR registry from patients who had not received Orencia during the study period. Analyses used propensity score matching and inverse probability of treatment weighting to help address the impact of selection bias.

Efficacy was based on OS at Day 180 post-HSCT. The OS rate at Day 180 in the Orencia in combination with CNI and MTX group was 98% (95% CI: 78, 100) and the OS rate at Day 180 in the CNI and MTX group was 75% (95% CI: 67, 82).

Chronic Graft Versus Host Disease (cGVHD)
The safety and efficacy of abatacept in the treatment of steroid-refractory cGVHD were evaluated in a phase I clinical trial involving 16 patients. (6) The study followed a 3+3 design with 2 escalating abatacept doses to determine the maximum tolerated dose (MTD). The partial response rate to abatacept was 44% and no dose-limiting toxicities were observed at the MTD of 10 mg/kg. The affected sites with greatest improvement were the mouth, GI tract, joints, skin, eyes, and lung. The most common adverse events were pulmonary infections (all of which resolved), diarrhea, and fatigue. Importantly, treatment with abatacept resulted in a 51% reduction in prednisone usage. These data suggest that abatacept is an effective treatment option for patients with steroid-refractory cGVHD.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) (7, 8)
According to the NCCN Drugs & Biologics Compendium, NCCN recommends (2A) abatacept for the treatment of: Chronic graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options.

Summary of Evidence
Based on the U.S. Food and Drug Administration (FDA) approved indications and a 2A National Comprehensive Cancer Network (NCCN) recommendation, Abatacept (Orencia®) may be considered medically necessary for the FDA labeled indications of moderately to severely active rheumatoid arthritis (RA) in adults; active psoriatic arthritis (PsA) in adults; moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in individuals 6 years of age or older; prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor; and for chronic graft-versus-host disease (cGVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options when the criteria are met. Abatacept (Orencia®) is considered experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0129

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2025	Document updated with literature review. The following changes were made to the Coverage section: 1) Criteria was added to the medically necessary coverage statement for the indication of moderately to severely active rheumatoid arthritis in adults, and 2) Moderately to severely active polyarticular juvenile idiopathic arthritis was changed from patients 2 years of age or older to individuals 6 years of age or older and criteria was added. Updated the following references: 1, 4, 7 and 8.
07/15/2023	Reviewed. No changes.
02/15/2023	Document updated with literature review. The following changes were made to the Coverage section: 1) Added NOTE 1; 2) Added "Abatacept (Orencia®) may be self-administered. Refer to the applicable pharmacy benefit plan when self-administered"; and 3) Added "Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor and chronic graft-versus-host disease (cGVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options" to the medically necessary coverage statement. References 6-8 added, and others updated.
09/15/2021	Reviewed. No changes.
10/01/2020	New medical document originating from RX501.051. Orencia® (Abatacept) may be considered medically necessary for the U.S. Food and Drug Administration (FDA) labeled indications of moderately to severely active rheumatoid arthritis (RA) in adults; active psoriatic arthritis (PsA) in adults; and moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age or older. The use of Orencia for all other indications is considered experimental, investigational and/or unproven.