Oscar Clinical Guideline: Zortress (everolimus) (PG033, Ver. 7)

Zortress (everolimus)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Zortress (everolimus), FDA-approved in 2009, is indicated for prophylaxis of organ rejection in adult patients. Everolimus inhibits the mammalian Target of Rapamycin (mTOR), a key regulatory kinase involved in activation and proliferation of T and B lymphocytes. Everolimus is available as 0.25mg, 0.5mg, 0.75mg, and 1mg strengths tablet forms. Zortress is considered medically necessary in specific circumstances related to organ transplantation.

Organ transplantation is the preferred treatment approach for end-stage kidney/liver diseases. It involves replacing the native organ with a supposedly healthy organ from another body. The recipient's immune system recognizes the foreign organ and attacks the foreign organ using its own immune system. Immunosuppressant drugs (such as Zortress) are used in organ transplant recipients to prevent the host from attacking the transplanted organ. This allows the recipient to live and function with the healthy, foreign organ.

Definitions

"Immunosuppressant" refers to a type of medication that modulates or suppresses the body's immune response. These drugs are critical in preventing the rejection of transplanted organs.

"mTOR (mammalian target of rapamycin) inhibitor" is a class of drugs that works by inhibiting the protein mTOR, which plays a key role in cell growth, cell proliferation, and the immune response. mTOR inhibitors are used in various medical conditions, including certain cancers and organ transplant rejection.

"Lymphocyte" is a subtype of white blood cell that plays a crucial role in the body's immune response. Lymphocytes, which include T cells and B cells, are involved in identifying and neutralizing foreign substances in the body.

Clinical Indications

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

The Plan considers Zortress (everolimus) medically necessary when ALL of the following criteria are met:

1. The member is 18 years of age or older; *AND*
2. The requested medication is being prescribed by, or in consultation with, a transplant specialist; *AND*
3. The member meets the medical necessity criteria for the applicable indication listed below:

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Kidney Transplant Rejection Prophylaxis

4. The member is at low-to-moderate immunologic risk; *AND*
5. The member meets ALL of the following:
    a. Has had Simulect (basiliximab) induction; *and*
    b. Is using Zortress (everolimus) concurrently with tacrolimus (reduced doses) or cyclosporine (reduced doses) and corticosteroids; *and*
    c. The member is unable to use, or has tried and failed ALL of the following:
        i. Calcineurin inhibitor (such as tacrolimus); *and*
        ii. Antiproliferative agent (such as mycophenolate); *and*
        iii. Sirolimus*; AND*
6. Clinical documentation has been provided for review to substantiate the above listed requirements.

Liver Transplant Rejection Prophylaxis

4. The member is at least 30 days post-transplant; *AND*
5. The member is using Zortress (everolimus) in combination with tacrolimus (reduced doses) or cyclosporine (reduced doses) , with or without corticosteroids; *AND*
6. The member is unable to use, or has tried and failed TWO (2) of the following:
    a. Calcineurin inhibitor (such as tacrolimus at a standard dose); *and/or*
    b. Antiproliferative agent (such as mycophenolate); *and/or*
    c. Sirolimus; *AND*
7. Clinical documentation has been provided for review to substantiate the above listed requirements.

Heart Transplant Rejection Prophylaxis

4. The member is at least 3 months post-transplant; *AND*
5. The member is using Zortress (everolimus) with reduced doses of an immunosuppressant; *AND*
6. The member is unable to use, or has tried and failed mycophenolate; *AND*
7. Clinical documentation has been provided for review to substantiate the above listed requirements.

Lung Transplant Rejection Prophylaxis

4. The member is at least 1 month post-transplant; *AND*
5. The member is using Zortress (everolimus) with concurrent corticosteroids and tacrolimus (reduced doses) or cyclosporine (reduced doses); *AND*
6. The member is unable to use, or has tried and failed both mycophenolate and azathioprine*; AND*

7. Clinical documentation has been provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Zortress (everolimus) will be approved up to a lifetime.

Experimental or Investigational / Not Medically Necessary

Zortress (everolimus) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Renal cell carcinoma (RCC). While everolimus is used for RCC, only Afinitor (everolimus) and Afinitor Disperz (everolimus) are approved for this indication.
- Advanced hormone receptor-positive, HER2 negative breast cancer. While everolimus is used for receptor-positive HER2 negative breast cancer, only Afinitor (everolimus) and Afinitor Disperz (everolimus) are approved for this indication.
- Progressive neuroendocrine tumors of pancreatic origin (PNET), progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. While everolimus is used for PNET AND NET of GI or lunch origin, only Afinitor (everolimus) and Afinitor Disperz (everolimus) are approved for this indication.
- Functional carcinoid tumors. While everolimus is used for functional carcinoid tumors, only Afinitor (everolimus) and Afinitor Disperz (everolimus) are approved for this indication.
- Renal angiomyolipoma and tuberous sclerosis complex (TSC). While everolimus is used for renal angiomyolipoma and TSC, only Afinitor (everolimus) and Afinitor Disperz (everolimus) are approved for this indication.

Appendix

Heart transplantation (≥3 months post-transplantation)

NOTE: The FDA issued a black box warning for Zortress (everolimus) because of the increased risk of mortality observed within the first three months post-transplantation among patients started on the higher dose (3 mg/day) of Zortress (everolimus) as de novo immunosuppression.

Zortress (everolimus) appears to be an effective medication for the prevention of cardiac allograft vasculopathy (CAV) and reducing rejection incidence in heart transplant patients, but its usage is recommended at least 3 months after transplantation due to increased risk of mortality within the first three months. Several studies indicate that everolimus, when administered in conjunction with reduced-dose cyclosporine, can reduce renal impairment post-transplant and decrease the incidence of CAV.

1. A clinical trial involving 634 de novo heart transplant recipients showed that those treated with everolimus (1.5 mg or 3.0 mg per day) had a smaller increase in coronary artery intimal thickness and intimal index compared to patients treated with azathioprine. This study also indicated that everolimus was associated with a significant reduction in the incidence of rejection. There were higher rates of bacterial infections (significant findings for the 3.0 mg group) and elevations in serum creatinine in the everolimus groups compared to the azathioprine group.
2. A large, 24-month, multicenter clinical trial involving 721 de novo cardiac transplant recipients compared the effects of everolimus (1.5 mg or 3 mg per day) with mycophenolate mofetil (MMF). The primary efficacy endpoint was a composite of the incidence of biopsy-proven acute rejection, acute rejection associated with hemodynamic compromise, graft loss/retransplant, death, or loss to follow-up. Everolimus 1.5 mg daily was noninferior to MMF at one year for the composite end point and for the incidence of biopsy-proven acute rejection. Mortality at one year was higher for the everolimus 3 mg daily group.
3. The SCHEDULE trial demonstrated that everolimus, in combination with reduced-dose cyclosporine and MMF, was effective at reducing the incidence and severity of cardiac allograft vasculopathy and improving renal function compared to continued cyclosporine use.

Lung transplantation (≥1 month post-transplantation)

Everolimus has been shown to be effective for prophylaxis of organ rejection in lung transplant recipients based on data from three prospective, randomized controlled trials. The drug is typically initiated at least 1 month post-transplant, in combination with concurrent corticosteroids and reduced doses of cyclosporine.

1. The data from these trials highlight both the benefits and risks of everolimus use. Some studies found that everolimus treatment resulted in fewer episodes of acute rejection and less deterioration in forced expiratory volume in one second (FEV1), a marker for chronic rejection. However, everolimus treatment also resulted in more adverse effects including serious bacterial and fungal infections, pneumonia, hyperlipidemia, anemia, and thrombocytopenia.
2. Trials comparing everolimus with other drugs such as azathioprine and mycophenolate found comparable efficacy in the prevention of bronchiolitis obliterans syndrome (BOS), but they also noted a higher rate of adverse events and drop-out rates with everolimus.
3. Several fatal cases of anastomotic bronchial dehiscence have been reported when sirolimus or everolimus was used in the first 30 to 90 days following lung transplantation. Thus, initiation of these drugs should be delayed until after the bronchial anastomosis is completely healed.
4. The addition of everolimus to standard calcineurin-based regimens (cyclosporine or tacrolimus) to mitigate nephrotoxicity did not demonstrate improved safety or outcomes. In fact, this strategy might even worsen outcomes by increasing thrombotic events and potential mortality.

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