Tacrolimus (extended-release)

Product:
TACROLIMUS (Advagraf®)
0.5mg, 1mg, 5mg extended-release capsules

Class of drugs:
Immunosuppressant

Indication:
Prevention of organ rejection in adult patients receiving allogeneic kidney transplant

Manufacturer:
Astellas Pharma Canada Inc.

CED Recommendation

The CED recommended that extended-release tacrolimus (Advagraf) not be funded, on the basis that this drug does not offer any therapeutic or cost advantage over existing alternatives.

Executive Officer Decision

Following the CED's recommendation and based on a subsequent pricing agreement with the manufacturer, the Executive Officer decided to list extended-release tacrolimus (Advagraf) on the Ontario Drug Benefit Formulary as a Limited Use benefit.

Status

Listed on the Ontario Drug Benefit Formulary as a Limited Use benefit.

Highlights of Recommendation:

- Studies demonstrate that extended-release tacrolimus is as safe and effective as standard tacrolimus in the prevention of graft rejection in kidney transplant patients.
- The once-daily dosing regimen may improve patient adherence to medication regimens but there is no direct evidence to show that extended-release tacrolimus actually improves patient adherence or other clinically important outcomes versus standard tacrolimus.
- Extended-release tacrolimus is currently priced the same as standard tacrolimus when compared on daily doses.
- **The CED noted that although extended-release tacrolimus is as safe and effective as standard tacrolimus, it does not offer any therapeutic or cost advantage over existing alternatives. Therefore, the CED recommended that this product not be funded.**

Background:

Chronic kidney failure leading to end-stage renal disease is a complication of many common medical conditions such as diabetes, hypertension or peripheral vascular disease. In addition to dialysis, kidney transplant is one of the ways to treat end-stage renal disease in patients with chronic kidney failure.

Patients who receive a transplanted kidney will reject the new organ because their immune system sees the new kidney as a foreign substance. To prevent rejection, kidney transplant recipients receive immunosuppressant drugs such as corticosteroids, cyclosporine, mycophenolate and tacrolimus to suppress this normal immune response.

Extended-release tacrolimus is the long-acting formulation of tacrolimus. It is taken once daily whereas the standard formulation of tacrolimus is taken twice daily. The standard formulation of tacrolimus is currently funded under the ODB Formulary as a Limited Use Benefit.

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Detailed Discussion:

- One pharmacokinetic study (Fitzsimmons et al. Yonsei Medical Journal 2004) compared extended-release tacrolimus given once daily to standard tacrolimus given twice daily and demonstrated that steady-state tacrolimus exposure of the extended-release formulation is equivalent to the standard formulation after a mg-for-mg conversion in stable post-transplant patients.
- In another small, open-label study (Alloway et al. Transplantation 2007), 67 kidney transplant recipients were safely converted, on a 1:1 mg basis of total daily dose, from standard tacrolimus twice daily to extended-release tacrolimus every morning and were safely maintained using the same therapeutic monitoring and post-transplant patient care techniques.
- A large, randomized, open-label study (Silva et al. Am J Transplantation 2007) evaluated the efficacy and safety of extended-release tacrolimus and standard tacrolimus compared to cyclosporine when given in combination with mycophenolate mofetil, corticosteroids and basiliximab induction in kidney transplant patients. The results of this study support the safety and efficacy of tacrolimus and are similar to that observed with cyclosporine when given in combination.
- Side effects observed with extended-release tacrolimus are similar to those for standard tacrolimus. These include hair loss, anemia, loss of appetite, diarrhea, high concentrations of potassium in the blood, high blood pressure, nausea, vomiting, tingling sensation in the extremities, itching, tremor, fever, headache, rash, high blood sugar concentrations, and abdominal pain.
- Since non-compliance with multiple dosing regimens can theoretically be a factor in graft rejection and late graft loss, a once-daily dosing regimen may improve patient adherence to medication regimens and therefore reduce graft rejection. However, there is no direct evidence that this long-acting formulation improves patient adherence or other clinically important clinical outcomes versus standard tacrolimus.
- Extended-release tacrolimus costs approximately $30 per day, depending on body weight. The price was the same as standard tacrolimus.
- **Overall, the CED noted that although extended-release tacrolimus is equivalent to standard tacrolimus with respect to safety and efficacy, it does not offer any therapeutic or cost advantage over existing alternatives and, therefore, recommended that this product not be funded.**

Funding Criteria:

Extended-release tacrolimus (Advagraf) is listed on the Ontario Drug Benefit Formulary as a Limited Use benefit according to the following clinical criterion:

For prophylaxis of organ rejection in adult patients receiving allogeneic kidney transplants.

CEDAC Recommendation:

(http://www.cadth.ca/index.php/en/cdr/recommendations)

The Canadian Expert Drug Advisory Committee (CEDAC) did not review extended-release tacrolimus (Advagraf).

Ontario

Ministry of
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