Bristol-Myers Squibb

Bristol-Myers Squibb Pharmaceuticals, South County Business Park, Leopardstown, Dublin 18, Ireland

14th March 2013

Direct Healthcare Professional Communication

Increased rate of acute graft rejection with Nulojix® (belatacept) associated with rapid corticosteroid taper in patients at high immunologic risk for acute rejection

Dear Healthcare Professional,

Bristol-Myers Squibb (BMS) in agreement with the European Medicines Agency (EMA) and the Irish Medicines Board (IMB) would like to inform you of the following:

Summary

- **In postmarketing experience, an increased rate of acute graft rejection has been reported with Nulojix® (belatacept) when corticosteroids have been rapidly tapered in patients at high immunologic risk for acute rejection**
- **Corticosteroid tapering should be implemented cautiously, particularly in patients with 4-6 human leukocyte antigen (HLA) mismatches**
- **The product information will be updated with**
  - **a warning on rapid tapering of corticosteroids in patients with high immunologic risk and**
  - **information on the corticosteroid doses used and the populations included in the clinical studies supporting the approval of Nulojix®**

Further information on the safety concern and the recommendation

Nulojix® in combination with corticosteroids and a mycophenolic acid is indicated for prophylaxis of graft rejection in adults receiving a renal transplant (see SmPC section 5.1 for data on renal function). It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

Nulojix® in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by week 6 post-transplant, has been associated with an increased rate of acute rejection, particularly Grade III rejection in the postmarketing setting. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches. This corticosteroid taper was more rapid than that used in the clinical studies supporting the approval of Nulojix®.

The product information of Nulojix® will be updated with a warning on the risk of acute graft rejection when corticosteroids are rapidly tapered. Information on the corticosteroid doses used and the populations included in the clinical studies supporting the approval of Nulojix® will also be added.

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Information on corticosteroid tapering used in clinical studies with Nulojix®

The safety and efficacy of belatacept as part of an immunosuppressive regimen following renal transplantation were assessed in 2 Phase III multicenter, controlled trials, studying two different dose regimens of belatacept (more intensive [MI] and less intensive [LI]) vs. cyclosporine, each in combination with basiliximab, MMF, and corticosteroids. NULOJIX® should be dosed according to the LI regimen. In both studies the doses of corticosteroids were tapered during the first 6 months following transplantation. In Study 1 (n=666 patients) the median corticosteroid doses administered with the Nulojix® recommended regimen up to months 1, 3, and 6 were 20 mg, 12 mg, and 10 mg, respectively. In Study 2 (n=543 patients), the median corticosteroid doses administered with the Nulojix® recommended regimen up to months 1, 3, and 6 were 21 mg, 13 mg, and 10 mg, respectively. Study 1 excluded recipients undergoing a first transplant whose current Panel Reactive Antibodies (PRA) were ≥50% and recipients undergoing a retransplantation whose current PRA were ≥30%, recipients when previous graft loss was due to acute rejection, and in case of a positive T-cell lymphocytotoxic cross match. Study 2 excluded recipients with a current PRA ≥30%, re-transplanted patients, and in case of a positive T-cell lymphocytotoxic cross match.

Call for reporting

Suspected adverse reactions should be reported to the IMB using an Adverse Reaction Report Form obtained either from the IMB or electronically via the website at www.imb.ie. Adverse reactions can also be reported to the IMB by calling on (01) 676 4971.

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Any suspected adverse reactions with Nulojix® (belatacept) may also be reported to BMS via telephone at 1 800 749 749 or via email at medical.information@bms.com.

Company contact point

If you have further questions or require additional information, please contact the BMS Medical Information department (telephone: 1 800 749 749; email: medical.information@bms.com).

Yours sincerely,

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