February 2023

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

To: *Physicians/Prescribers in transplant centers in Israel who may perform HSCT*
From: *BMS Israel Medical director*

Subject: **PTLD or CMV reactivation in Patients Undergoing Unrelated-Donor Hematopoietic Stem Cell Transplantation (HSCT) with Intravenous ORENCIA in Israel**

תקציר:
מכתב זה לצוות הרפואי מביל מידע לגבי האפשרות להתפרצות של EBV או CMV בזמן שימוש באורנסיה (abatacept) במטופלים העוברים השתלת תאי גזע של מערכת הדם (HSCT). המכתב יופץ לרופאים במרכזי השתלה בישראל.

בשימוש ב abatacept בשילוב עם methotrexate (MTX) ומעכבי calcineurin (CNI) למניעת מחלת שתל נגד מאכסן חריפה (aGVHD), תתכן התפרצות של CMV או EBV כמו גם סיבובים נילווים, זיהום CMV פולשני או Post-transplant lymphoproliferative disease (PTLD). יש לשקול ניטור לזיהוי התפרצות CMV או EBV כמו גם מתן טיפול מונע.

מחקר פאזה II שביסס את השימוש של abatacept במניעת aGVHD עקב אחר התפרצות EBV ו CMV במטופלים בהתאם לפרקטיקות טיפוליות הנהוגות במרכז הרפואי. לפני תחילת הטיפול באורנסיה מומלץ מתן של טיפול אנטי ויראלי למניעת התפרצות EBV למשך 6 חודשים מזמן ההשתלה למניעת EBV-associated PTLD. כמו כן מומלץ לעקוב אחר מטופלים למשך 6 חודשים מזמן ההשתלה לצורך זיהוי זיהום או התפרצות של CMV, ללא תלות בתוצאות הבדיקות הסרולוגיות לגילוי נגיף ה-CMV שבוצעו טרם ההשתלה, הן של התורם והן של הנתרם. יש לשקול מתן טיפול מונע לזיהום או התפרצות של נגיף ה- CMV.

Further details:
Bristol-Myers Squibb as requested by the Israel Ministry of Health, is issuing a Direct Healthcare Professional Communication (DHPC) in Israel to communicate important safety information regarding ORENCIA IV for prophylaxis of acute graft versus host disease (aGVHD) in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 6 years of age or older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor. The DHPC is being distributed to transplant centers in Israel who perform HSCT from a matched or 1 allele-mismatched unrelated-donor and other appropriate healthcare professionals.

In a study in adults and children above the age of 6 undergoing unrelated-donor HSCT with ORENCIA IV, reactivation of Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) were reported.

Post-Transplant Lymphoproliferative Disorder (PTLD) occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 4 patients (3.4%) experienced PTLD. All the PTLD events were associated with EBV infection. Three of the four patients were EBV serology positive at baseline; one patient had negative baseline EBV serology with donor EBV serology unknown. Three of the 4 patients discontinued acyclovir prophylaxis at day 30 post-transplant. The range of time to onset of the events was 49 to 89 days post-transplant. Monitor patients for EBV reactivation in accordance with institutional practices.

Before administering ORENCIA, administer recommended antiviral prophylactic treatment for Epstein-Barr Virus (EBV) reactivation, and continue for six months following HSCT to prevent EBV-associated PTLD.

CMV invasive disease occurred in patients who received ORENCIA for aGVHD prophylaxis during unrelated HSCT. Of 116 patients who received ORENCIA, 7% experienced CMV invasive diseases up to day 225 post-transplant. All the patients who experienced CMV invasive disease were CMV serology positive at baseline. The median time to onset of the event was 91 days post-transplant. CMV invasive diseases predominantly involved the gastrointestinal tract.

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Monitor patients for CMV infection/reactivation for 6 months post-transplant regardless of the results of donor and recipient pre-transplant CMV serology.

Consider prophylactic antivirals for Cytomegalovirus (CMV) infection/reactivation during treatment and for six months following HSCT.

Please refer to the PRODUCT INFORMATION, for a complete discussion of the INDICATIONS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE and ADMINISTRATION.
Link to Orencia Prescribing Information:
https://mohpublic.z6.web.core.windows.net/IsraelDrugs/Rishum01_5_947785522.pdf

Bristol-Myers Squibb is committed to ensuring *Orencia* is used safely and in accordance with the Product Labeling. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
If you have further questions, require additional information or would like to report adverse events to BMS, please contact *BMS MEDICAL INFORMATION DEPARTMENT* at *1809-388-054 (a toll free number) or medinfo.Israel@bms.com*

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