Report DARZALEX® Daratumumab

Product& Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance:daratumumab **Brand Name:**DARZALEX® **Originator/licensee:** Janssen-Cilag International NV **Classification:** NI **ATC code:**L01XC24 **Orphan Status:** **Eu:**Yes **Us:**- **Mechanism of action:**daratumumab is an IgG1κ human mAb that binds to the CD38 protein expressed at a high level on the surface of MM tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity [1].	**Authorized Indication:** **EMA:** in combination with pomalidomide and dexamethasone for the treatment of adult pts with MM [2]: • who have received one prior therapy containing a PI and lenalidomide and were lenalidomide-refractory; • who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated PD on or after the last therapy. **Route of administration:**SC **Licensing status** **EU CHMP P.O. date:**20/5/2021 **FDA M.A. date:**- **EU Speed Approval Pathway:**Yes **FDA Speed Approval Pathway:**- **ABBREVIATIONS:** **AEs:** Adverse Events **AL:** amyloid light-chain **CD38**: Cluster of Differentiation 38 **CHMP:** Committee for Medicinal Products for Human Use **CI**: Confidence Interval **DaraKd**: Daratumumab, Carfilzomib, dexamethasone **DaraPomDex:** Daratumumab, Pomalidomide and low-dose Dexamethasone **DP**: Disease Progression **EloPd:**Elotuzumab, Pomalidomide, Dexamethasone **HR:** Hazard Ratio **IgG1κ**: Humanized Immunoglobulin G, subclass 1, κ light chain **IsaKd:**Isatuximab, Carfilzomib, dexamethasone **IsaPd:**Isatuximab, Pomalidomide, Dexamethasone **IRRs:** Infusion-Related Reactions **IV:**Intravenous **M.A.:** Marketing Authorization **mAb:**monoclonal antibody **MM**: Multiple Myeloma **PFS:** Progression Free Survival **PI:** Proteasome Inhibitor **P.O.:** Positive Opinion **PomDex:** Pomalidomide and low-dose Dexamethasone **PomVd**: Pomalidomide, Bortezomib, dexamethasone **pts:** patients **QW:** Once a Week **Q2W:** Every 2 Weeks **Q4W**: Every 4 Weeks **SC**: Subcutaneous **TEAEs:** Treatment Emergent Adverse Events	**Summary of clinical EFFICACY:** **APOLLO (NCT03180736):** is amulticenter, phase III, randomized, open-label study comparing DaraPomDex with PomDex in adult pts with relapsed or refractory MM who have received at least one prior treatment regimen with both lenalidomide and a PI and have demonstratedDP. Subjects (n = 304) were randomized in a 1:1 ratio to receive either DaraPomDex or PomDex until DPor unacceptable toxicity. *Experimental arm: (n=151)* ● **Daratumumab**: 16 mg/kg as an IV infusion or 1,800 mg SC QW for eight weeks, then Q2W for an additional 16 weeks, then Q4W thereafter. ● **Pomalidomide**: 4 mgorallyon days 1 through 21 of each 28-day cycle. ● **Dexamethasone**: 40 mg (20 mg for pts ≥75 years of age) orally, once daily, on day 1, 8, 15, 22 of each 28-day treatment cycle. *Active comparator arm: (n=153)* ● **Pomalidomide:** 4 mg orally on days 1 through 21 of each 28-day cycle. ● **Dexamethasone:**40 mg (20 mg for pts ≥75 years of age) orally, once daily, on day 1, 8, 15, 22 of each 28-day treatment cycle. The primary endpoint was comparison of PFS between treatment arms. PFS was assessed monthly from randomization until DP or death, whichever occurred first (approximately up to three years). ParaPomDex reduced the risk of DPor death by 37% (HR, 0.63; 95.5 CI, 0.47-0.85; p=0.0018).The median PFS for the DaraPomDex and PomDex arms were reported to be 12.4 and 6.9 months, respectively [3-4]. **Summary of clinical SAFETY:** The most common grade 3/4 AEs with a >5% difference between ParaPomDex vs.PomDex armswere neutropenia (68% vs. 51%), leukopenia (17% vs. 5%), lymphopenia (12% vs. 3%), febrile neutropenia (9% vs. 3%), and pneumonia (13% vs. 7%).The most common serious TEAEs reported were pneumonia (13% and 7%) and lower respiratory tract infection (11% and 9%). The rate of IRRs with SC daratumumab was low (6%, all grade 1/2), and 2% of pts had local injection-site reactions (all grade 1) [4-5]. **Ongoing studies:** • ***For the same indication:***Yes • ***For other indications:***Yes [Phase III, but if it is an O/OE drug, also Phase II] **Discontinued studies (for the same indication):**No **References:** 1. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/darzalex-2 3. https://www.clinicaltrials.gov/ct2/show/NCT03180736 4. https://adisinsight.springer.com/trials/700284521 5. https://ash.confex.com/ash/2020/webprogram/Paper135874.html 6. https://www.drugs.com/price-guide/darzalex-faspro 7. Usmani S.Z. Hoering A. Cavo M. et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma – an IMWG Research Project. Blood Cancer J. 2018; 8: 123 8. M.A. Dimopoulos, P. Moreau, E. Terpos et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†, Annals of Oncology, Volume 32, Issue 3, 2021, Pages 309-32 9. https://clinicaltrials.gov/ct2/results?cond=&term=daratumumab&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&type=Intr&phase=1&phase=2 10. https://adisinsight.springer.com/drugs/800041859 11. https://clinicaltrials.gov/ct2/results?cond=Myeloma+Multiple&term=refractory&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&type=Intr&phase=1&phase=2	**Cost of Therapy:** The price (USA) for daratumumab 1,800 mg, 15 ml, is $8,296.30 [6]. The price for one cycle of therapy (administered QW for 28 days) is: $ 33,185.20 **Epidemiology:** MM is a plasma cell neoplasm that accounts for 1%-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100,000/year. Despite the significant improvement in pts' survival over the past 20 years, only 10-15% of pts achieve or exceed expected survival compared with the matched general population [7]. ----- **POSSIBLE PLACE IN THERAPY** **Pts who have received one prior line of therapy:** PomVd, DaraKdorIsaKd are recommendedtherapies for pts who were previously exposed orarerefractory to lenalidomide, while DaraKd or IsaKd can alsobe given in pts who are refractory to bortezomib. **Pts at third and subsequent lines of treatment:**for pts who have been exposed or are refractory toboth bortezomib and lenalidomide, DaraKd, IsaPd, IsaKdorEloPd are recommended [8]. **OTHER INDICATIONS IN DEVELOPMENT:** Plasma Cell Myeloma, Systemic Lupus Erythematosus, Lupus Nephritis, Refractory T-Cell Lymphoma Relapsed T-Cell Lymphoma [9]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:**in combination with bortezomib, melphalan and prednisone or lenalidomide and dexamethasone in pts with MM who are ineligible for autologous stem cell transplant [10]. **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Isatuximab, carfilzomib, venetoclax, pomalidomide [11]. *Service reorganization Y/N: No *Possible off label use Y/N: Yes

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