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 N.V. **Classification:** NI **ATC code:** L01FC01 **Orphan Status:** **Eu:** Yes **Us:** / **Mechanism of action:** Daratumumab is a monoclonal antibody that has been designed to attach to the protein CD38, which is found in high amounts on abnormal white blood cells in multiple myeloma and AL amyloidosis. By attaching to CD38 on these cells, daratumumab activates the immune system to kill the abnormal white blood cells. [1].	**Authorized Indication:** **EMA**: Daratumumab as monotherapy is indicated for the treatment of adults with SMM at high risk of developing MM [1]. **FDA:** / **Route of administration:** SC **Licensing status** **EU CHMP P.O. date:** 19/06/2025 **FDA M.A. date:** / **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** / --- **ABBREVIATIONS:** **AE**: Adverse Event **AL amyloidosis**: amyloid light chain or primary amyloidosis **CHMP**: Committee for Medicinal Products for Human Use **CI**: Confidential Interval **ECOG**: Eastern Cooperative Oncology Group **HR**: Hazard Ratio **IMWG:** International myeloma working group **M.A.:** Marketing Authorization **MM**: Multiple myeloma **NR**: Not reached **PFS**: Progression-Free Survival **P.O.**: Positive Opinion **PS**: Performance Status **Pts**: Patients **SAE**: Serious adverse events **SC**: Subcutaneously **SMM**: Smouldering multiple myeloma **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **AQUILA (NCT03301220)** was an open label, multicentre, randomized, phase III trial to assess the efficacy of daratumumab for high-risk SMM, a precursor disease of active MM for which no treatments have been approved. Pts. ≥ 18 years of age with a confirmed diagnosis of SMM, according to IMWG criteria, within the previous five years were eligible. Pts. had to have measurable disease and an ECOG PS of 0 or 1. Pts. were required to be at high risk for progression to active MM (% of clonal plasma cells in bone marrow of ≥10% and the presence of ≥1 risk factors, including a serum M-protein level of ≥30 g/liter, IgA SMM, immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes, a ratio of involved free light chains to uninvolved free light chains in serum of 8 to less than 100, or a percentage of clonal plasma cells in bone marrow of >50% to <60%). Pts. (n=) were randomly assigned in a 1:1 ration to receive SC daratumumab monotherapy (n=) or active monitoring (n=). Daratumumab 1800 mg co-formulated with recombinant human hyaluronidase was administered on a weekly basis in cycles 1 and 2, and 2, every 2 weeks in cycles 3 through 6, and every 4 weeks thereafter in 28-day cycles. Treatment was continued for 39 cycles, for 36 months, or until confirmation of disease progression, whichever occurred first. The primary endpoint was PFS in the ITT population. After a median follow-up of 65.2 months, progression to active MM or death had occurred in 67 pts. (34.5%) in the daratumumab group and in 99 pts. (50.5%) in the active monitoring group (HR, 0.49; 95% CI, 0.36 to 0.67; P<0.001). PFS at 5 years was 63.1% in the daratumumab group, as compared with 40.8% in the active-monitoring group [2]. **Summary of clinical SAFETY:** Grade 3 or 4 AEs occurred in 40.4% and 30.1% of the pts. in the daratumumab group and the active-monitoring group, respectively; the most common grade 3 or 4 AE was hypertension (5.7% vs. 4.6%). SAEs occurred in 29.0% and 19.4% of the pts. in the daratumumab group and the active-monitoring group, respectively; the most common SAE was pneumonia (3.6% vs. 0.5%). AEs that led to treatment discontinuation occurred in 11 pts. (5.7%) in the daratumumab group. AEs that led to death occurred in two pts. (1.0%) in the daratumumab group (Covid-19 and Covid-19 pneumonia) and in four pts. (2.0%) in the active-monitoring group (pulmonary oedema, cardiac arrest, pulmonary embolism, and cardiac failure) [2]. **Ongoing studies:** ● ***For the same indication:*** No ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex [2] https://www.nejm.org/doi/full/10.1056/NEJMoa2409029 [3] https://gallery.farmadati.it/Home.aspx [4] https://www.osservatoriomalattierare.it/i-tumori-rari/mieloma-multiplo [5] https://www.nature.com/articles/bcj2016100 [6] https://www.nature.com/articles/s41408-022-00719-0	**Cost of therapy:** In Italy, 100 mg of DARZALEX® concentrate for infusion cost € 425 (ex-factory price) [3] **Epidemiology:** In Italy 5,600 new cases of active MM each year are estimated, with an incidence of about 8.75 per 100,000 inhabitants per year, and an overall prevalence of approximately 30,000 pts. undergoing treatment or monitoring [4]. According to international studies, SMM accounts for about 13–14% of new MM cases [5]. ---- **POSSIBLE PLACE IN THERAPY**: For pts. with newly diagnosed high-risk SMM, therapy with lenalidomide or lenalidomide plus dexamethasone (Rd) for two years, or enrolment in clinical trials, is recommended. The choice between lenalidomide and Rd should consider pt's age, comorbidities, and tolerance to dexamethasone. Early intervention is recommended. Pts. diagnosed several years earlier, who have remained stable without therapy may continue observation, with intervention only in the event of changes in laboratory parameters indicating disease progression [6]. The addition of Daratumumab to these regimens could represent a new opportunity for these pts. **OTHER INDICATIONS IN DEVELOPMENT:** Neuromyelitis Optica Spectrum Disorders (NCT05403138) **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Denosumab (NCT03839459); isatuximab + lenalidomide + dexamethasone (NCT04270409). *Service reorganization: No *Possible off label use: Yes

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