Daratumumab (Darzalex®) in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Daratumumab is a human monoclonal antibody targeting CD38.	Daratumumab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received one prior therapy containing a proteasome inhibitor (PI) and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy.

Current treatment [3]

- NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:
  - In instances of the first relapse, the guidelines recommend the use of:
    - Daratumumab plus bortezomib plus dexamethasone.
    - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
    - Bortezomib monotherapy – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.
  - Subsequent relapse treatment may include:
    - Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
    - Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy.
    - Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
    - Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
    - Daratumumab monotherapy for adults whose previous therapy included a PI and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

Regulatory status

EMA [2]

Approval status for this indication: On 20 May 2021, the CHMP adopted a positive opinion recommending changes to the terms of the marketing authorisation for Darzalex®.

The CHMP extended the existing indication for Darzalex® 1,800 mg solution for injection (active substance: daratumumab; excipients: recombinant human hyaluronidase rHuPH20, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injections) as follows:

- Darzalex® is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received one prior therapy containing a PI and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy.

Other indications:

- MM**:** Darzalex® is indicated
  - in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed MM who are ineligible for autologous stem cell transplant.
  - in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM who are eligible for autologous stem cell transplant.

FDA [4-7]

On 9 July 2021, the FDA approved daratumumab and hyaluronidase-fihj (Darzalex FASPRO®, injection, for **subcutaneous use**) in combination with pomalidomide and dexamethasone for adult patients with MM who have received at least one prior line of therapy including lenalidomide and a PI.

Other indications: Darzalex FASPRO® is indicated for the treatment of adult patients with:

- MM in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- MM in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory MM who have received at least one prior therapy.
- MM in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
- MM in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- MM as monotherapy, in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent
- AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients (indication approved under accelerated approval based on response rate).

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

❖ AL Amyloidosis

- Darzalex® is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

❖ Limitations of Use: Darzalex FASPRO® is not indicated and is not recommended for the treatment of patients with AL amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

✓ **Orphan status**
✓ **Medicine under additional monitoring**
✓ **Accelerated assessment**[1]

Costs [8]

Darzalex® concentrate for solution for infusion 400 mg, 20 mg/ml **= € 2,096.00** (ex-factory price)
1 vial Darzalex® solution for injection 1,800 mg/15ml**= € 6,288.00** (ex-factory price)

Warnings and precautions [6]

Darzalex FASPRO®:

❖ **Hypersensitivity and other administration reactions**: Permanently discontinue Darzalex FASPRO® for life-threatening reactions.
❖ **Cardiac toxicity in patients with AL amyloidosis**: Monitor patients with cardiac involvement more frequently for cardiac adverse reactions and administer supportive care as appropriate.
❖ **Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding Darzalex FASPRO® to allow recovery of neutrophils.
❖ **Thrombocytopenia**: Monitor complete blood cell counts periodically during treatment. Consider withholding Darzalex FASPRO® to allow recovery of platelets.
❖ **Embryo-foetal toxicity**: Can cause foetal harm. Advise pregnant women of the potential risk to a foetus and advise females of reproductive potential to use effective contraception.
❖ **Interference with cross-matching and red blood cell antibody screening**: Type and screen patients prior to starting treatment. Inform blood banks that a patient has received Darzalex FASPRO®.

Pre-/Post-medication (Darzalex Faspro®) [9]

❖ Darzalex® solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions.
❖ Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections.
❖ If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. Darzalex® therapy should be discontinued immediately and permanently.
❖ To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following Darzalex® injection.
❖ Patients with a history of the chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Study characteristics: APOLLO trial [10-12]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
APOLLO, Study MMY3013	304	pomalidomide + dexamethasone + daratumumab	pomalidomide +	PFS in the ITT population	ongoing, open-label, randomised, phase 3 trial	-	European Myeloma Network and Janssen Research and Development	[11]

[1] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

NCT03180736		(1800 mg subcutaneously or 16 mg/kg IV)[2]	dexamethasone[3]					

Efficacy (I vs. C)	Safety (I vs. C)
Median PFS: 12.4 months (95% CI: 8.3–19.3) vs. 6.9 months (5.5–9.3); HR 0.63; 95% CI: 0.47–0.85, two-sided p=0.0018 **Kaplan-Meier estimate of the percentage of patients who were alive without disease progression at 18 months**: 42% (95% CI: 34–50) vs. 26% (18–33) **Overall response**: 69% (95% CI: 61–76) vs. 46% (95% CI: 38–55); odds ratio 2.7; 95% CI: 1.7–4.4; p<0.0001 **Complete response or better**: 25% vs. 4%; odds ratio 8.2; 95% CI: 3.4–20.3; p<0.0001 **Stringent complete response**: 9% vs. 1% **Complete response**: 15% vs. 3% **Very good partial response or better**: 51% vs. 20%; odds ratio 4.3; 95% CI: 2.6-7.3; p<0.0001 **Very good partial response**: 26% vs. 16% **Partial response:** 18% vs. 27% **Minimal response**: 7% vs. 10% **Stable disease**: 17% vs. 32% **Progressive disease:** 3% vs. 5% **Response could not be evaluated**: 4% vs. 7% **Negative status for minimal residual disease**: 9% vs. 2%; odds ratio 4.7; 95% CI: 1.3–16.9; p=0.010 **The median time to first response**: 1.0 month (95% CI: 1.0–1.1) vs. 1.9 months (1.0–2.0) **Median duration of response:** not reached (95% CI: 15.2–not reached) vs. 15.9 months (8.3–24.8) **OS data at the time of the PFS analysis were immature:** 32% and 33% of patients died **Median time to subsequent antimyeloma therapy**: 23.2 months (95% CI: 13.8–not estimable) vs. 11.8 months (8.9–15.4) **Median PFS after the next line of therapy:** not reached (95% CI: 16.6–not estimable) vs. 17.6 months (13.4–not estimable); 57 (38%) vs. 66 (43%) progression events; HR 0.79; 95% CI: 0.55–1.14; p=0.21	**Any TEAE Grade 3**: n=47/149 (31.5%) vs. n=82/150 (54.7%) **Any TEAE Grade 4:** n=73/149 (49.0%) vs. n=30/150 (20.0%) **SAEs:** n=75/149 (50%) vs. n=59/150 (39%) **Serious TRAEs:** n=40/149 (27%) vs. n=15/150 (10%) **Discontinuation of the trial treatment due to an AE**: n=3/149 (2%) vs. n=4/150 (3%) **AEs that resulted in death[4]:** n=11/149 (7%) vs. n=11/150 (7%)

Risk of bias (study level) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	No, open-label	unclear[5]	yes[6]	unclear

Study characteristics: EQUULEUS trial [1, 14]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EQUULEUS, MMY1001	103	daratumumab 16 mg/kg +	-	Safety	open-label, multicentre, multiarm, phase 1b study	-	Janssen Research & Development	[1]

[2] Oral pomalidomide (4 mg, once daily on days 1–21) + oral dexamethasone (40 mg once daily on days 1, 8, 15, and 22; 20 mg for those aged 75 years or older) at each 28-day cycle + daratumumab (1800 mg subcutaneously or 16 mg/kg IV) weekly during cycles 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter until disease progression or unacceptable toxicity.

[3] Oral pomalidomide (4 mg, once daily on days 1–21) + oral dexamethasone (40 mg once daily on days 1, 8, 15, and 22; 20 mg for those aged 75 years or older) at each 28-day cycle.

[4] The most common AE leading to death was pneumonia: 2% vs. 1% of patients in the respective groups. In the daratumumab plus pomalidomide and dexamethasone group, 5 AEs leading to death were deemed possibly or probably related to daratumumab and pomalidomide; no AEs leading to death were deemed related to treatment in the pomalidomide and dexamethasone group.

[5] APOLLO trial is ongoing until 06/2022.

[6] Partly industry-funded.

NCT01998971		pomalidomide 4 mg daily for 21 days of each 28-day cycle + dexamethasone 40 mg weekly						

Efficacy (I vs. C)	**Safety** (I vs. C)
ORR: 60% (95% CI: 50.1%-69.7%); ORR was generally consistent across pre-specified subgroups stratified by age, race, renal function, refractory status, type of myeloma, and cytogenetic risk. **Best response of stringent CR, CR, VGPR and PR** in 8%, 9%, 25%, and 18% of patients, respectively. **Clinical benefit rate**: 62% (with 2% of patients with a minimal response) **Stable disease**: 25% **Progressive disease**: 3% **Median duration of response**: not estimable (NE; 95% CI, 13.6-NE months) **6- and 12-month disease-progression–free rates** (among responders): 85% (95% CI: 72.4-91.7) and 68% (53.2-78.8), respectively. **Median (range) time to first response**: 1.0 month (0.9-2.9) **Time to best response**: 2.3 months (0.9-12.5) **Median time to CR or better** was longer (5.9 months), consistent with prior studies of daratumumab monotherapy in heavily treated patients. **Median PFS**: 8.8 months (95% CI: 4.6-15.4) **12-month PFS rate**: 42% (31.5-51.9) **Median time to progression**: 10.4 months (95% CI: 6.7-NE). **Median OS** (at a median follow-up of 13.1 months): 17.5 months (13.3-NE) **Estimated survival rates at 3, 6, and 12 months**: 89% (95% CI: 81.2-93.8), 79% (69.3-85.6), and 66% (55.6-74.8), respectively.	**Grade 3/4 AEs**: n=99% **Serious TEAEs** occurred in 53% of patients, 25% of which were considered **related to a study drug** and 18% of which were deemed **related to daratumumab**. **Discontinuation due to TEAEs:** 16%; 8% of discontinuations were considered related to a study drug, and 3% were considered related to daratumumab. **IRRs:** in 50% of patients **Deaths:** 9% of patients died during treatment or within 30 days of receiving their last dose of the study drug. Overall, no deaths were considered to be related to daratumumab.

Risk of bias (study level) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
Not appropriate, single-arm study	Not appropriate, single-arm study	No, open-label	unclear[7]	yes[8]	**unclear**

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, IRRS=infusion-related reactions, ITT=intention-to-treat, MG=median gain, MM=multiple myeloma, n=number of patients, NICE=National Institute for Health and Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event, VGPR=very good partial response

References:

[7] EQUULEUS trial is ongoing until 07/2022.
[8] The study design and analyses were devised by the investigators and sponsor. Final data analysis and verification of accuracy were conducted by the sponsor. Writing assistance was funded by Janssen Global Services.

1. Chari A, Suvannasankha A, Fay JW, Arnulf B, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017;130(8):974-981. [Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5570682/].
2. European Medicines Agency (EMA). Medicines. Darzalex. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/darzalex-2].
3. National Institute for Health Research (NIHR). Daratumumab in addition to pomalidomide and dexamethasone for relapsed or refractory multiple myeloma. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2020/03/20467-Daratumumab-Pomalidomide-Dexamethasone-for-Multiple-Myeloma-V1.0-FEB2020-NON-CONF.pdf].
4. The ASCO Post. FDA Approves Daratumumab in Combination With Pomalidomide and Dexamethasone for Relapsed or Refractory Multiple Myeloma. [Available from: https://ascopost.com/News/57747].
5. U.S. Food and Drug Administration (FDA). Darzalex. Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761036s035lbl.pdf].
6. U.S. Food and Drug Administration (FDA). Darzalex FASPRO. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761145s007lbl.pdf].
7. U.S. Food and Drug Administration (FDA). FDA approves daratumumab and hyaluronidase-fihj with pomalidomide and dexamethasone for multiple myeloma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-pomalidomide-and-dexamethasone-multiple-myeloma].
8. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
9. European Medicines Agency (EMA). Darzalex: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf].
10. Supplement to: Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol 2021; 22: 801–12.
11. Dimopoulos MA, Terpos E, Boccadoro M, Delimpasi S, Beksac M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol 2021; 22: 801–12. [Available from: https://linkinghub.elsevier.com/retrieve/pii/s1470204521001285].
12. U.S. National Library of Medicine, ClinicalTrials.gov. Comparison of Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Previously Treated With Lenalidomide and a Proteasome InhibitorDaratumumab/Pomalidomide/Dexamethasone vs Pomalidomide/Dexamethasone (EMN14). [Available from: https://clinicaltrials.gov/ct2/show/NCT03180736].
13. European Network for Health Technology Assessment (EUnetHTA). LEVELS OF EVIDENCE. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
14. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of JNJ-54767414 (HuMax CD38) (Anti-CD38 Monoclonal Antibody) in Combination With Backbone Treatments for the Treatment of Patients With Multiple Myeloma. [Available from: https://clinicaltrials.gov/ct2/show/NCT01998971?term=nct01998971&draw=2&rank=1].