Daratumumab (Darzalex®) in a new pharmaceutical form associated with a new strength and a new route of administration for the treatment of multiple myeloma

General information

Drug description	Indication
Human IgGκ CD38-targeting monoclonal antibody	New pharmaceutical form, new strength and new route of administration of daratumumab

Current pharmaceutical form/strength/route of administration [1]

DARZALEX® 20 mg/ml concentrate for solution for infusion.
Each 5 ml vial contains 100 mg of daratumumab (20 mg daratumumab per ml).
Each 20 ml vial contains 400 mg of daratumumab (20 mg daratumumab per ml).

Regulatory status

EMA [2]

Approval status for this indication: On 30 April 2020, the CHMP recommended the addition of a new pharmaceutical form (solution for injection) of daratumumab, associated with a new strength (1800 mg in 15-ml vial) and a new route of administration (subcutaneous injection into the abdomen).

Indications:
The new formulation can be used for all the authorised indications of Darzalex®, as follows:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma (MM) who are ineligible for autologous stem cell transplant (ASCT)
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM who are eligible for ASCT
- 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 proteasome inhibitor (PI) and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

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

FDA [3]

Approval status for this indication: Approved 05/2020: DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use;

1,800 mg daratumumab and 30,000 units hyaluronidase per 15 ml (120 mg and 2,000 units/ml) solution in a single-dose vial

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 ASCT
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with relapsed or refractory MM who have received at least one prior therapy
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- 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.

Costs

Darzalex® solution for injection 1800 mg = € 6,288.00 (ex-factory price) [4]

COLUMBA trial patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles) until progressive disease or toxicity. Patients received a median of six cycles per group.

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	PEs (co-primary)	Characteristics	Biomarker	Funding	Publication(s)

[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.

COLUMBA NCT03277105 MMY3012	522	1800 mg of subcutaneous daratumumab co-formulated with rHuPH20 2000 U/mL	16 mg/kg of intravenous daratumumab	- overall response (partial response or better) - maximum trough concentration (C_{trough})	ongoing[2], multicentre, open-label, non-inferiority, randomized phase 3 trial	-	Janssen Research & Development	Link

Efficacy (I vs. C)	**Safety** (I vs. C)
Overall response: 41% vs. 37% (relative risk 1.11, 95% CI 0.89–1.37) CR or better: 1.9% vs. 2.7% Very good partial response: 17.1% vs. 14.3% Partial response: 22.1% vs. 20.1% **C_{trough}:** the geometric means ratio for C_{trough} was 107.93% (90% CI 95.74–121.67), and the maximum C_{trough} was 593 µg/ml (SD 306) in the subcutaneous group and 522 µg/ml (226) in the intravenous group Rate of infusion-related reaction: 12.7% vs. 34.5% Median PFS: 5.59 months vs. 6.08 months, HR 0.99 (95% CI 0.78-1.26) **CTSQ**: mean scores for the "Satisfaction with therapy" domain were consistently higher in I than in C. Patients in the subcutaneous group responded more positively to individual components of "Satisfied with form of cancer therapy (intravenous/subcutaneous)", "Taking cancer therapy as difficult as expected", and "Were side effects as expected" than those in the intravenous group.	**Grade ≥3 treatment-emergent AEs**: n=119/260 (46%) vs. n=126/258 (49%) **SAEs**: n=68/260 (26%) vs. n=76/258 (29%) **Death[3]:** n=1/260 (0.4%) vs. and n=4/258 (1.6%) **Discontinuation due to AEs:** n=18/260 (7%) vs. n=21 (8%)

ESMO-MCBS version 1.1

Not applicable

Risk of bias (study level)

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	open-label	unclear[4]	yes[5]	high risk

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Abbreviations: AE=adverse event, ASCT= autologous stem cell transplant, CHMP - Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CTSQ= Cancer Therapy Satisfaction Questionnaire, C_{trough}=maximum trough concentration, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HR=hazard ratio, MM=multiple myeloma, n=number, SAE=serious adverse event, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, QoL=quality of life

References:

1. 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.
2. European Medicines Agency (EMA). Medicines.Darzalex. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/darzalex-1.
3. U.S. Food and Drug Administration (FDA). Drugs@FDA.Darzalex Faspro.Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761145s000lbl.pdf.
4. Apotheker-Verlag Ö. Warenverzeichnis online [Available from: https://warenverzeichnis.apoverlag.at/.

[2] COLUMBA trial is ongoing until 12/2023
[3] Death judged to be treatment-related
[4] COLUMBA trial is currently ongoing
[5] Industry-funded; trial was designed by the study sponsor

5. Mateos M, Nahi H, Legiec W, Grosicki S, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial Lancet Haematol 2020. Published Online March 23, 2020 [Available from: https://www.sciencedirect.com/science/article/abs/pii/S2352302620300703.