

04-2025

חופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: דארזלקס 120 מ"ג/מ"ל תת עורי 1,800 מ"ג
Darzalex 120mg/ml S.C 1800mg

חברת J-C Health Care Ltd מבקשת להודיעכם כי העלון לרופא של התכשיר שבנדון התעדכן ב-04-2025.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט **בחול עם קו** **חוצה**, טקסט המהווה חמרה מודגש **ברקע צהוב**), אך קיימים עדכונים נוספים.

ההתוויות המאושרות לתכשיר בישראל:

Multiple myeloma

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (see section 5.1).
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Light chain (AL) amyloidosis

In combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

מרכיב פעיל: Daratumumab

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
<https://israel drugs.health.gov.il/#!/byDrug>

כמו כן, מצורפים לפרסום זה וניתן לקבל העתק מודפס שלהם באמצעות פנייה לבעל הרישום: J-C Health Care Ltd, קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,

יעל לפידות מללי
רוקח/ת ממונה

J-C Health Care Ltd

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 97% (74102/8321380) of patients experienced an IRR. Most IRRs occurred following the first injection and were grade 1-2. IRRs occurring with subsequent injections were seen in 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 2.93-2 hours (range 0.1-50.08-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in 1% of patients.

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4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions of any grade (≥ 20 % patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy, and upper respiratory tract infection, musculoskeletal pain and COVID-19. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea, atrial fibrillation and syncope.

The safety profile of the DARZALEX subcutaneous formulation was similar to that of intravenous formulation with the exception of a lower rate of IRRs. In the phase III study MMY3012, neutropenia was the only adverse reaction reported at $\geq 5\%$ higher frequency for DARZALEX subcutaneous formulation compared to intravenous daratumumab (grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions

Table 6 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab.

The data reflects exposure to DARZALEX subcutaneous formulation (1800 mg) in 6391187 patients with multiple myeloma (MM). The data includes 260 patients from a phase III active-controlled study (MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy, and 149 patients from a phase III active-controlled study (MMY3013) who received DARZALEX subcutaneous formulation in combination with pomalidomide and dexamethasone (D-Pd). The data also reflects three open-label, clinical studies in which patients received DARZALEX solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX solution for subcutaneous injection in combination with either bortezomib, melphalan and prednisone (D-VMP, n=67), lenalidomide and dexamethasone (D-Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n=67). Additionally, data reflect exposure to 193 patients with newly diagnosed AL amyloidosis from a phase III active-controlled study (AMY3001) in which patients received DARZALEX subcutaneous formulation in combination with bortezomib, cyclophosphamide and dexamethasone (D-Vcd).

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received

intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$) and very rare ($< 1/10000$). ~~Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.~~

Table 6: Adverse reactions in multiple myeloma and AL amyloidosis patients treated with intravenous daratumumab or subcutaneous daratumumab

System organ class	Adverse reaction	Frequency	Incidence (%)	
			Any grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection ^a	Very common	3745	33
	COVID-19 ^{a,g}		26	7
	Pneumonia ^a		1719	1011
	Bronchitis ^a		14	1
	Urinary tract infection	Common	68	1
	Influenza		4	1 [#]
	Sepsis ^a		4	34
	COVID-19 ^e		7	4
	Cytomegalovirus infection ^a	Uncommon	< 1	< 1 [#]
Hepatitis B Virus reactivation ^a	< 1		< 1	
Blood and lymphatic system disorders	Neutropenia ^a	Very common	3943	3337
	Thrombocytopenia ^a		2932	1719
	Anaemia ^a		27	1211
	Lymphopenia ^a		1413	1110
	Leukopenia ^a		11	6
Immune system disorders	Hypogammaglobulinemia ^a	Common	23	< 1 [#]
	Anaphylactic reaction ^b	Rare	-	-
Metabolism and nutrition disorders	Hypokalaemia ^a	Very common	11	3
	Decreased appetite		10	1
	Hyperglycaemia	Common	67	3
	Hypocalcaemia		56	1
	Dehydration		2	1 [#]
Psychiatric disorders	Insomnia	Very common	1517	1 [#]
Nervous system disorders	Peripheral sensory neuropathy	Very common	2633	43
	Headache		10	< 1 [#]
	Dizziness	Common	9	< 1 [#]
	Paraesthesia		9	< 1
	Syncope		3	2 [#]
Cardiac disorders	Atrial fibrillation	Common	34	1
Vascular disorders	Hypertension ^a	Common	9	4
Respiratory, thoracic and mediastinal disorders	Cough ^a	Very common	2122	< 1 [#]
	Dyspnoea ^a		18	2
	Pulmonary oedema ^a	Common	1	< 1
Gastrointestinal disorders	Diarrhoea	Very common	2933	45
	Constipation		2829	1
	Nausea		22	1 [#]
	Abdominal pain ^a		13	1
	Vomiting		1413	1 [#]
	Pancreatitis ^a	Common	1	1

Skin and subcutaneous tissue disorders	Rash	Very common	1012	1 [#]
	Pruritus	Common	6	<1 [#]
Musculoskeletal and connective tissue disorders	Back Musculoskeletal pain ^g	Very common	1635	23
	Arthralgia		14	1
	Muscle spasms		1112	<1 [#]
	Arthralgia		10	<1 [#]
	Musculoskeletal chest pain	Common	6	<1 [#]
General disorders and administration site conditions	Fatigue	Very common	2324	4
	Oedema peripheral ^a		2224	1
	Pyrexia		2122	1
	Asthenia		1819	2
	Chills	Common	8	<1 [#]
	Injection site reactions ^{d,e}		8	0
Injury, poisoning and procedural complications	Infusion-related reactions ^c			
	Daratumumab intravenous ^f	Very common	39	5
	Daratumumab subcutaneous ^e	Common	97	1 [#]

[#] No grade 4

^a Indicates a grouping of terms.

^b Based on post-marketing adverse reactions.

^c Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.

^d Injection site reactions includes terms determined by investigators as related to injection of daratumumab.

^e Frequency based on daratumumab subcutaneous studies only (N=8321380).

^f Frequency based on daratumumab intravenous studies only (N=2324).

~~Note: Based on 3156 multiple myeloma and AL amyloidosis patients treated with daratumumab intravenous or daratumumab subcutaneous.~~

^g Incidence is based on a subset of patients who received at least one dose of study treatment on or after 01 February 2020 (the start of the COVID-19 pandemic) from studies MMY3003, MMY3006, MMY3008 and MMY3013, and all daratumumab treated patients from studies MMY3014 and MMY3019 (N=984).

~~Note: Based on 3704 multiple myeloma and AL amyloidosis patients treated with daratumumab intravenous or daratumumab subcutaneous.~~

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=8321380) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was 8.26.4% with the first injection of DARZALEX (1800 mg, week 1), 0.43% with the week 2 injection, and 1.42% with subsequent injections. Grades 3 and 4 IRRs were seen in 0.87% and 0.1% of patients, respectively. No patients had grade 4 IRRs.

Signs and symptoms of IRR may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, blurred vision and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma) (see section 4.4).

Injection site reactions (ISRs)

In clinical studies (N=8321380) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was 7.78%. There were no grade 3 or 4 ISRs. The most common (≥ 1%) ISR at the site of injection was erythema and rash.

Infections

In patients with multiple myeloma receiving daratumumab as monotherapy, the overall incidence of infections was similar between DARZALEX subcutaneous formulation (52.9%) versus intravenous

daratumumab groups (50.0%). Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX subcutaneous formulation (11.7%) and intravenous daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported grade 3 or 4 infection across studies. In active-controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients. Fatal infections were primarily due to pneumonia and sepsis.

In patients with multiple myeloma receiving intravenous daratumumab combination therapy, the following were reported

Grade 3 or 4 infections:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Grade 5 (fatal) infections:

Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

In patients with multiple myeloma receiving DARZALEX subcutaneous formulation combination therapy, the following were reported:

Grade 3 or 4 infections: DPd: 28%, Pd: 23%

Grade 5 (fatal) infections: DPd: 5%, Pd: 3%

Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

In patients with AL amyloidosis receiving DARZALEX subcutaneous formulation combination therapy, the following were reported:

Grade 3 or 4 infections: D-VCd: 17%, VCd: 10%

Grade 5 infections: D-VCd: 1%, VCd: 1%

Key: D=daratumumab; VCd=bortezomib-cyclophosphamide-dexamethasone

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Cardiac disorders and AL amyloidosis-related cardiomyopathy

The majority of patients in AMY3001 had AL amyloidosis-related cardiomyopathy at baseline (D-VCd 72% vs. VCd 71%). Grade 3 or 4 cardiac disorders occurred in 11% of D-VCd patients compared to 10% of VCd patients, while serious cardiac disorders occurred in 16% vs. 13% of D-VCd and VCd patients, respectively. Serious cardiac disorders occurring in $\geq 2\%$ of patients included cardiac failure (D-VCd 6.2% vs. VCd 4.3%), cardiac arrest (D-VCd 3.6% vs. VCd 1.6%) and atrial fibrillation (D-VCd 2.1% vs. VCd 1.1%). All D-VCd patients who experienced serious or fatal cardiac disorders had AL amyloidosis-related cardiomyopathy at baseline. The longer median duration of treatment in the D-VCd arm compared to the VCd arm (9.6 months vs. 5.3 months, respectively) should be taken into consideration when comparing the frequency of cardiac disorders between the two treatment groups. Exposure-adjusted incidence rates (number of patients with the event per 100 patient-months at risk) of overall grade 3 or 4 cardiac disorders (1.2 vs. 2.3), cardiac failure (0.5 vs. 0.6), cardiac arrest (0.1 vs. 0.0) and atrial fibrillation (0.2 vs. 0.1) were comparable in the D-VCd arm vs. the VCd arm, respectively.

With a median follow-up of 11.4 months, overall deaths (D-VCd 14% vs. VCd 15%) in study AMY3001 were primarily due to AL amyloidosis-related cardiomyopathy in both treatment arms.

Other special populations

In the phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients

Of the ~~3549~~ 4238 patients who received daratumumab (n=~~832~~ 1422 subcutaneous; n=~~2717~~ 2816 intravenous) at the recommended dose, 38% were 65 to less than 75 years of age, and 165% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1976), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who ~~are~~ were ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplant (n=351), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma for whom transplant was not planned as initial therapy or who were ineligible for autologous stem cell transplant (n=197), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with newly diagnosed AL amyloidosis (n=193), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia.