J-C Health Care Ltd.

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08-2021

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא של התכשיר:

Darzalex 120mg/ml S.C 1800mg

המאושר להתוויות הבאות:

- 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.
- 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.

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

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. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea ~~and~~ atrial fibrillation and syncope.~~.~~

With the exception of IRRs (see Table 5 below), the safety profile of ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at ≥ 5% higher frequency for ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions
Table 5 summarises the adverse reactions that occurred in patients receiving ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation or intravenous formulation of daratumumab.

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The data reflects exposure to ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation (1,800 mg) in 490 patients with multiple myeloma (MM) including 260 patients from a Phase III active-controlled trial (Study MMY3012) who received ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG solution for subcutaneous injection as monotherapy and three open-label, clinical studies in which patients received ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG 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).

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions in multiple myeloma 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	38%	2%
	Bronchitis[a]	Very Common	14%	2%
	Pneumonia[a]	Very Common	14%	9%
	Urinary tract infection	Common	7%	1%
	Influenza	Common	4%	1%[#]
	Sepsis[a]	Common	4%	3%
	Cytomegalovirus infection[a]	Common	1%	<1%[#]
	Hepatitis B Virus reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders	Neutropenia[a]	Very Common	40%	33%
	Thrombocytopenia[a]	Very Common	30%	18%
	Anaemia[a]	Very Common	27%	12%
	Lymphopenia[a]	Very Common	13%	11%
	Leukopenia[a]	Very Common	11%	6%
Immune system disorders	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	10%	1%
	Hyperglycaemia	Common	6%	3%
	Hypocalcaemia	Common	5%	1%
	Dehydration	Common	2%	1%[#]
Psychiatric disorders	Insomnia	Very Common	14%	1%[#]
Nervous system disorders	Peripheral sensory neuropathy	Very Common	26%	3%
	Headache	Very Common	11%	<1%[#]
	Dizziness	Common	9%	<1%[#]
	Paraesthesia	Common	9%	<1%
	Syncope	Common	3	2[#]

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Cardiac disorders	Atrial fibrillation	Common	3%	1%
Vascular disorders	Hypertension[a]	Very Common	10%	5%
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very Common	22%	<1%[#]
	Dyspnoea[a]	Very Common	18%	2%
	Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1%[#]
	Vomiting	Very Common	14%	1%[#]
	Pancreatitis[a]	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1%[#]
	Pruritus	Common	5%	<1%[#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1%[#]
	Arthralgia	Very Common	10%	1%[#]
	Musculoskeletal chest pain	Common	6%	<1%[#]
General disorders and administration site conditions	Fatigue	Very Common	23%	3%
	Oedema peripheral[a]	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1%[#]
	Injection site erythema[e]	Common	4%	0
	Injection site reactions[d,e]	Common	8%	0
Injury, poisoning and procedural complications	Infusion-related reactions[c]			
	Daratumumab intravenous[f]	Very Common	39%	5%
	Daratumumab subcutaneous[e]	Very Common	11%	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=490).
[f] Frequency based on daratumumab intravenous studies only (N=2324).
Note: Based on 2814 multiple myeloma 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=490) with ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation, the incidence of any grade IRRs was 10.2% with the first injection of ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG (1,800 mg, Week 1), 0.2% with the Week 2 injection, and 0.8% with subsequent injections. Grade 3 IRRs were seen in 1.4% of patients. 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, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.4).

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Injection site reactions (ISRs)
In clinical studies (N=490) with ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation, the incidence of any grade injection site reaction was 8.2%. There were no Grade 3 or 4 ISRs. The most common (≥1%) ISRs were erythema, injection site induration, pruritis.

Infections
In patients receiving ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG ~~subcutaneous formulation~~ daratumumab as monotherapy, the overall incidence of infections was similar between ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG subcutaneous formulation (52.9%) versus intravenous daratumumab groups (50.0%). ~~Additionally,~~ Grade 3 or 4 infections also occurred at similar frequencies between ~~DARZALEX~~DARZALEX 120MG/ML S.C. 1,800MG 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 severe (Grade 3 or 4) infection across studies.

In patients receiving intravenous daratumumab combination therapy, ~~Grade 3 or 4 infections~~the following ~~were reported as follows~~: Grade 3 or 4 infections:
Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.
Pneumonia was the most commonly reported severe (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 receiving intravenous daratumumab combination therapy, fatal infections (Grade 5) were reported as follows:
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%.
Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-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.

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 3207 patients who received daratumumab (n=490 subcutaneous; n=2717 intravenous) at the recommended dose, 38% were 65 to 75 years of age, and 17% 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=1827), 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 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.

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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il/)

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העלון לרופא נשלח לפרסום במלואו למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלו מודפס בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה