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 ובעלון לצרכן של התכשיר:
העדכון כולל תוספת התוויה ושינוי במשטר המינון, כמפורט מטה.

# Darzalex 20mg/ml IV

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:**

## 4.4 Special warnings and precautions for use

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

Infusion-related reactions
~~DARZALEX~~DARZALEX 20MG/ML I.V can cause serious IRRs, including anaphylactic reactions (see section 4.8). These reactions can be life-threatening and fatal outcomes have been reported.

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## 4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions of any grade (≥ 20% patients) were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

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Tabulated list of adverse reactions

Table 6 summarises the adverse reactions that occurred in patients receiving ~~DARZALEX~~DARZALEX 20MG/ML I.V. The data reflects exposure to ~~DARZALEX~~DARZALEX 20MG/ML I.V (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received ~~DARZALEX~~DARZALEX 20MG/ML I.V in combination with background regimens and 156 patients who received ~~DARZALEX~~DARZALEX 20MG/ML I.V as monotherapy. Post-marketing adverse reactions are also included.

In Study MMY3006, the number of CD34+ cell yield was numerically lower in the D-VTd arm compared with the VTd arm (Median: D-VTd: 6.3 x $10^6$/kg; VTd 8.9 x $10^6$/kg) and among those who completed mobilisation, more patients in the D-VTd group received plerixafor compared to those in the VTd arm (D-VTd: 21.7%; VTd: 7.9%). The rates of engraftment and haematopoietic reconstitution was similar among the transplanted subjects in the D-VTd and VTd arms (D-VTd: 99.8%; VTd: 99.6%; as measured by the recovery of neutrophils > 0.5 x $10^9$/L, leukocytes > 1.0 x $10^9$/L, and platelets > 50 x $10^9$/L without transfusion).
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 6: Adverse reactions in multiple myeloma patients treated with ~~DARZALEX~~DARZALEX 20MG/ML I.V 16 mg/kg**

| System Organ Class | Adverse reaction | Frequency | Incidence (%) | |
|---|---|---|---|---|
| | | | Any Grade | Grade 3-4 |
| **Infections and infestations** | ~~Pneumonia~~[a] Upper respiratory tract infection[a] | Very Common | ~~16~~41 | ~~10~~3 |
| | Bronchitis[a] | | 17 | 2 |
| | ~~Upper respiratory tract infection~~[a]Pneumonia[a] | | ~~41~~16 | ~~3~~10 |
| | Urinary tract infection | Common | 8 | 1 |
| | Influenza | | 5 | 1* |
| | Sepsis[a] | | 4 | 4 |
| | Cytomegalovirus infection[a] | | 1 | <1* |
| | Hepatitis B Virus reactivation[b] | Uncommon | - | - |
| **Blood and lymphatic system disorders** | Neutropenia[a] | Very Common | 44 | 39 |
| | Thrombocytopenia[a] | | 31 | 19 |
| | Anaemia[a] | | 27 | 12 |
| | Lymphopenia[a] | | 14 | 11 |
| | Leukopenia[a] | | 12 | 6 |
| **Immune system disorders** | Anaphylactic reaction[b] | Rare | - | - |
| **Metabolism and nutrition disorders** | Decreased appetite | Very Common | 12 | 1 |
| | Hyperglycaemia | Common | 7 | 3 |
| | Hypocalcaemia | | 6 | 1 |
| | Dehydration | | 3 | 1* |
| **Nervous system disorders** | Peripheral sensory neuropathy | Very Common | 32 | 3 |
| | ~~Paraesthesia~~Headache | | ~~11~~12 | <1* |

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| | | | | |
|---|---|---|---|---|
| | ~~Headache~~Paraesthesia | | ~~12~~11 | <1~~*~~ |
| | Syncope | Common | 2 | 2* |
| **Cardiac disorders** | Atrial fibrillation | Common | 4 | 1 |
| **Vascular disorders** | Hypertension[a] | Very Common | 10 | 5 |
| **Respiratory, thoracic and mediastinal disorders** | Cough[a] | Very Common | 25 | <1* |
| | Dyspnoea[a] | | 21 | 3 |
| | Pulmonary oedema[a] | Common | 1 | <1 |
| **Gastrointestinal disorders** | ~~Diarrhoea~~Constipation | Very Common | ~~32~~33 | ~~4~~1 |
| | ~~Constipation~~Diarrhoea | | ~~33~~32 | ~~1~~4 |
| | Nausea | | 26 | 2* |
| | Vomiting | | 16 | 1* |
| | Pancreatitis[a] | Common | 1 | 1 |
| **Musculoskeletal and connective tissue disorders** | Back pain | Very Common | 18 | 2 |
| | Muscle spasms | | 14 | <1* |
| **General disorders and administration site conditions** | Fatigue | Very Common | 26 | 4 |
| | Oedema peripheral[a] | | 26 | 1 |
| | Pyrexia | | 23 | 2 |
| | Asthenia | | 21 | 2 |
| | Chills | Common | 9 | <1* |
| **Injury, poisoning and procedural complications** | Infusion-related reaction[c] | Very Common | 40 | 4 |

* No Grade 4

[a] Indicates grouping of terms

[b] Post-marketing adverse reaction

[c] Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=2066) the incidence of any grade IRRs was 37% with the first (16 mg/kg, Week 1) infusion of ~~DARZALEX~~DARZALEX 20MG/ML I.V, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 IRR with the Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st Week, 2nd Week and subsequent infusions were approximately 7, 4 and 3 hours respectively.

Severe IRRs included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse IRRs included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4).

When ~~DARZALEX~~DARZALEX 20MG/ML I.V dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of ~~DARZALEX~~DARZALEX 20MG/ML I.V the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last ~~DARZALEX~~DARZALEX 20MG/ML I.V infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of ~~DARZALEX~~DARZALEX 20MG/ML I.V following ASCT were consistent in terms of symptoms and severity (Grade 3/4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

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In Study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade IRRs was 42%, with 36% of patients experiencing IRRs on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections

In patients receiving ~~DARZALEX~~DARZALEX 20MG/ML I.V combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 2~~7~~8%, 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 ~~DARZALEX~~DARZALEX 20MG/ML I.V 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 2459 patients who received ~~DARZALEX~~DARZALEX 20MG/ML I.V at the recommended dose, 38% were 65 to 75 years of age, and 15% 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=1 213), 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=710), the most common serious adverse reaction that occurred more frequently in elderly (≥75 years of age) was pneumonia.

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## 5.1 Pharmacodynamic properties

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Combination treatment with bortezomib:

Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with ~~DARZALEX~~DARZALEX 20MG/ML I.V 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous ~~infusion~~ injection at a dose of 1.3 mg/m$^2$ body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of ~~DARZALEX~~DARZALEX 20MG/ML I.V infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medicinal product. ~~DARZALEX~~DARZALEX 20MG/ML I.V treatment was continued until disease progression or unacceptable toxicity.

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**השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:**

**אזהרות מיוחדות הנוגעות לשימוש בתרופה:**

**לפני הטיפול ב~~דארזלקס~~דארזלקס 20 מ"ג/מ"ל תוך ורידי, פנה לרופא או לאחות במקרים הבאים:**

תגובות הנובעות מהעירוי

~~דארזלקס~~דארזלקס 20 מ"ג/מ"ל תוך ורידי ניתנת בעירוי (טפטוף) לווריד. לפני ולאחר כל עירוי של ~~דארזלקס~~דארזלקס 20 מ"ג/מ"ל תוך ורידי, יינתנו לך תרופות שמטרתן להקטין את הסיכוי לתגובות הנובעות מהעירוי (ראה סעיף 3 – "תרופות הניתנות במהלך הטיפול ב~~דארזלקס~~דארזלקס 20 מ"ג/מ"ל תוך ורידי"). תגובות אלה עלולות להתרחש במהלך העירוי או במהלך 3 הימים לאחר העירוי.

במקרים מסוימים ייתכן ותסבול מתגובה אלרגית חמורה, אשר עלולה להתבטא בהתנפחות הפנים, השפתיים, הפה, הלשון או הגרון, בקשיי בליעה או נשימה או בפריחה מגרדת (חרלת). חלק ממקרי האלרגיה החמורה או תופעות לוואי אחרות חמורות הקשורות לעירוי הסתיימו במוות.

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**4. תופעות לוואי**

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תופעות לוואי שכיחות (common) – תופעות שמופיעות ב- 1-10 משתמשים מתוך 100

- הפרעות בקצב הלב (פרפור פרוזדורים)
- צבירת נוזלים בריאות אשר גורמת לקוצר נשימה
- שפעת
- זיהום בדרכי השתן
- זיהום חמור בכל הגוף (ספסיס)
- התייבשות
- התעלפות
- רמה גבוהה של סוכר בדם
- רמה נמוכה של סידן בדם
- לבלב מודלק

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כמו כן נוספו הנחיות שימוש לצוות הרפואי בעלון לצרכן.

העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה