แบบ ย. ๕

FORM MA-5

เลขรับที่ 15040/62 (NB)
วันที่ 1 มี.ค. 2562
ลงชื่อ ..... ผู้รับคำขอ

คำขอแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยา

ข้าพเจ้า นายนรเทพ เอี่ยมแก้ว ผู้รับอนุญาต/ผู้ดำเนินกิจการ ตามใบอนุญาต

[ ] ผลิตยา [✓] นำหรือสั่งยาเข้ามาในราชอาณาจักร

[✓] แผนปัจจุบัน [ ] แผนโบราณ

ใบอนุญาตเลขที่ 209/2526 ในนามของ (บริษัท/~~ห้าง/ร้าน~~) แจนเซ่น-ซีแลก จำกัด

ขอแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยาชื่อ ตามเอกสารแนบหมายเลข ๑ เลขทะเบียนที่ ตามเอกสารแนบหมายเลข ๑

รายการที่ขอแก้ไขเปลี่ยนแปลง (ระบุ) ตามเอกสารแนบหมายเลข ๑

ข้าพเจ้าได้แนบเอกสารหรือหลักฐานตามที่สำนักงานคณะกรรมการอาหารและยาประกาศกำหนดมาพร้อมด้วยแล้ว และขอรับรองว่าข้อความอื่นใดที่ไม่ได้ระบุไว้ในคำขอฉบับนี้เหมือนเดิมทุกประการและขอยกเลิกรายการเดิมในทะเบียนตำรับยา ตั้งแต่วันที่ได้รับอนุญาตให้แก้ไขเปลี่ยนแปลงรายการดังกล่าวในทะเบียนตำรับยา เว้นแต่พนักงานเจ้าหน้าที่จะมีคำสั่งเป็นอย่างอื่น

(ลายมือชื่อ) ..... ผู้รับอนุญาต

(นายนรเทพ เอี่ยมแก้ว) (ตัวบรรจง)

(ลายมือชื่อ) ..... ผู้มีหน้าที่ปฏิบัติการ

(นางสาวจิตราวรรณ อดิศัยภารดี) (ตัวบรรจง)

(ยื่นแบบคำขอพร้อมสำเนาคู่ฉบับ)

(ส่วนนี้สำหรับเจ้าหน้าที่)

Received: 18 Jun 19

คำสั่งพนักงานเจ้าหน้าที่

[✓] อนุญาต

[ ] ไม่อนุญาต เนื่องจาก

[ ] คำสั่งอื่น

(ลายมือชื่อ) .....

(นางสาววรสุดา ยูงทอง)

ตำแหน่ง ผู้อำนวยการกองส่งเสริมการประกอบการผลิตภัณฑ์สุขภาพ

พนักงานเจ้าหน้าที่

ลงวันที่ 10 พ.ค. 2562

ให้ใช้ ☐ฉลาก ☑เอกสารกำกับยา ฉบับเดิมต่อไป ได้อีก 6 เดือน นับจากวันที่ได้รับอนุญาต

RECEIVED 18 JUN 2019

Nakarin Yano

รายละเอียดการแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยา

- การแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยาตามแบบ ย. ๕ เลขรับที่ 15040/62 (NB)

ชื่อยา ตามเอกสารแนบหมายเลข ๑ เลขทะเบียนที่ ตามเอกสารแนบหมายเลข ๑

รายการที่ขอแก้ไขเปลี่ยนแปลง

[ ] ฉลาก
[✓] เอกสารกำกับยา
[ ] ขนาดบรรจุ
[ ] ชื่อยา
[ ] ลักษณะยา
[ ] สูตรยา (แสดงรายละเอียดการแก้ไขเปลี่ยนแปลงสูตรตำรับยา)
[ ] วิธีวิเคราะห์และข้อกำหนดมาตรฐาน
(แสดงรายละเอียดการแก้ไขเปลี่ยนแปลงวิธีวิเคราะห์และข้อกำหนดมาตรฐาน)
[ ] อื่น ๆ เกี่ยวกับผลิตภัณฑ์ยา

ขอแก้ไขเปลี่ยนแปลง จาก เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ ชุดที่ได้รับอนุมัติฉบับล่าสุด (USPI version May 2018) เมื่อวันที่ 10 ก.ย. 2561

ที่เคยได้รับอนุมัติไว้

เป็น เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ ที่เพิ่มข้อมูลขนาดยาและวิธีการใช้ยาแบบแบ่งขนาดยา ดังนี้ “To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively” ตาม USPI ฉบับใหม่ (ข้อความที่เพิ่มจากเดิม แสดงด้วยตัวหนังสือสีน้ำเงินขีดเส้นใต้ และข้อความที่ตัดออกจากเดิม แสดงด้วย~~ตัวหนังสือสีแดงขีดฆ่า~~)

เป็นการขอแก้ไขเปลี่ยนแปลง

[✓] ยาแผนปัจจุบัน
[✓] ตาม ASEAN Variation Guideline (AVG) [✓] MaV 1 [ ] MiV-PA [ ] MiV-N
[ ] นอกเหนือจากที่กำหนดไว้ใน ASEAN Variation Guideline (AVG)

[ ] ยาแผนโบราณ

- เอกสารหลักฐาน

[✓] สำเนาใบสำคัญการขึ้นทะเบียนตำรับยาหรือใบแทน
[✓] สำเนาใบอนุญาต
[✓] เอกสารสนับสนุนการขอแก้ไขเปลี่ยนแปลง
[✓] เอกสารตาม AVG
[ ] กรณีที่นอกเหนือ AVG
[ ] ยาแผนโบราณ
[ ] รายละเอียดการแก้ไขเปลี่ยนแปลงสูตรตำรับยา
[ ] รายละเอียดการแก้ไขเปลี่ยนแปลงวิธีวิเคราะห์ข้อกำหนดมาตรฐาน
[ ] อื่น ๆ

รายการคำขอแก้ไขเปลี่ยนแปลงรายการในทะเบียนตำรับยาที่ต้องการยื่น

รายการ	ประเภทยา	ชื่อยา	เลขทะเบียนที่	รายละเอียดการแก้ไขเปลี่ยนแปลง	ประเภทตาม AVG	ประเภท EC Variation
1	ยาชีววัตถุ	DARZALEX	1C 30/60 (NBC)	เพิ่มข้อมูลวิธีการใช้ยา “To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively” (รายละเอียดตามแบบ ย. ๕ หน้า ๒)	MaV-1	-
2	ยาชีววัตถุ	DARZALEX	1C 31/60 (NBC)	เพิ่มข้อมูลวิธีการใช้ยา “To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively” (รายละเอียดตามแบบ ย. ๕ หน้า ๒)	MaV-1	-

การแก้ไขเปลี่ยนแปลงระดับหลัก - Major Variation (MaV)	
MaV-1	**การแก้ไขเปลี่ยนแปลงและ/หรือการเพิ่มข้อบ่งใช้ ขนาดและแผนการให้ยา กลุ่มผู้ป่วย หรือข้อมูลทางด้านคลินิกซึ่งเป็นการขยายการใช้ยา**
เงื่อนไขในการยื่นขอแก้ไขเปลี่ยนแปลง	1. ฉลากและเอกสารกำกับยา ในที่นี้ หมายถึง เอกสารกำกับยา (Package insert) เอกสารกำกับยาสำหรับผู้ป่วย ฉลากบนกล่องบรรจุยา/บรรจุภัณฑ์ ฉลากยาด้านใน และ/หรือ ฉลากยาบนบลิสเตอร์หรือสตริป 2. เป็นการแก้ไขเปลี่ยนแปลงที่สืบเนื่องมาจากการเปลี่ยนแปลงข้อมูลสรุปของผลิตภัณฑ์ตามแบบ Summary of Product Characteristics (SmPC) หรือเอกสารอื่นๆที่เทียบเท่า เช่น เอกสาร USPI
เอกสารที่ต้องยื่นเพื่อประกอบการพิจารณา	1. ฉลากและเอกสารกำกับยาฉบับที่ได้รับอนุญาต ณ ปัจจุบัน 2. ฉลากและเอกสารกำกับยาที่ขอแก้ไขเปลี่ยนแปลง และฉบับที่แสดงการเปรียบเทียบข้อความที่ขอแก้ไขให้ชัดเจน 3.เอกสารแสดงเหตุผลในการขอแก้ไขเปลี่ยนแปลง 4. รายงานของผู้เชี่ยวชาญทางคลินิก (Clinical expert reports) และ/หรือรายงานการศึกษาวิจัยทางคลินิก (ในกรณีที่เกี่ยวข้อง) 5. เอกสารกำกับยา (Package insert) ข้อมูลสรุปของผลิตภัณฑ์ตามแบบ Summary of Product Characteristics (SmPC) หรือเอกสารกำกับยาสำหรับผู้ป่วยที่ได้รับอนุญาตจากหน่วยงานกำกับดูแลยาที่อ้างอิง หรือประเทศผู้ผลิตซึ่งระบุข้อความที่ขอแก้ไขเปลี่ยนแปลง (ในกรณีที่เกี่ยวข้อง) 6 หนังสืออนุญาตจากประเทศผู้ผลิตหรือประเทศอ้างอิง ซึ่งอนุญาตข้อบ่งใช้ใหม่ หรือขนาดและแผนการให้ยาใหม่ (ในกรณีที่เกี่ยวข้อง) 7. เอกสารหลักฐานแสดงข้อมูลการศึกษาทางคลินิก ตามคู่มือหลักเกณฑ์การขึ้นทะเบียนตำรับยาแบบ ASEAN (ACTD) ส่วนที่ 4 (ในกรณีที่เกี่ยวข้อง)

เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

DARZALEX™

FULL PRESCRIBING INFORMATION

1. Name of the Medicinal Product

1.1 Product Name

DARZALEX™ (daratumumab)

1.2 Strength

DARZALEX is a colorless to pale yellow, preservative-free solution available as:
Injection:

- 100 mg/5 mL (20 mg/mL) in a single-dose vial.
- 400 mg/20 mL (20 mg/mL) in a single-dose vial.

1.3 Pharmaceutical Dosage Form

Concentration for solution for infusion

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

2.2 Quantitative Declaration

Each DARZALEX single-dose 20 mL vial contains 400 mg daratumumab
Each DARZALEX single-dose 5 mL vial contains 100 mg daratumumab

3. Pharmaceutical Form

DARZALEX is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. The pH is 5.5. DARZALEX must be diluted with 0.9% Sodium Chloride Injection, USP.

4. Clinical Particulars

4.1 Therapeutic indication

DARZALEX is indicated:

- in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

4.2 Posology and method of administration

4.2.1 Recommended Dose and Schedule

- Administer pre-infusion and post-infusion medications *[see Recommended Concomitant Medications]*.
- Administer only as an intravenous infusion after dilution in 0.9% Sodium Chloride Injection, USP *[see Preparation for Administration and Administration]*.
- DARZALEX should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur *[see Infusion Reactions]*.

Newly Diagnosed Multiple Myeloma

Dosing Schedule for DARZALEX in Combination with Bortezomib, Melphalan and Prednisone (6-week cycle regimen) for Patients Ineligible for Autologous Stem Cell Transplant

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP], 6-week cycle dosing regimen)

Weeks	**Schedule**
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54[a]	every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 7

[b] First dose of the every-4-week dosing schedule is given at Week 55

For dosing instructions of combination agents administered with DARZALEX *see Clinical Studies.*

Relapsed/Refractory Multiple Myeloma

Monotherapy and Combination Therapy with Lenalidomide or Pomalidomide and Low-Dose Dexamethasone (4-week cycle regimens)

The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 2:

Table 2: DARZALEX dosing schedule for monotherapy and in combination with lenalidomide or pomalidomide (4-week cycle dosing regimens)

Weeks	**Schedule**
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at Week 9

[b] First dose of the every-4-week dosing schedule is given at Week 25

For dosing instructions of combination agents administered with DARZALEX, *see Clinical Studies* and manufacturer's prescribing information.

Combination Therapy with Bortezomib and Dexamethasone (3-week cycle regimen)
The recommended dose of DARZALEX is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedule in Table 3:

Table 3: DARZALEX dosing schedule with bortezomib (3-week cycle dosing regimen)

Weeks	**Schedule**
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 10

[b] First dose of the every-4-week dosing schedule is given at Week 25

For dosing instructions of combination agents administered with DARZALEX *see Clinical Studies* and manufacturer's prescribing information.

Missed DARZALEX Doses
If a planned dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Infusion Rates and Management of Infusion Reactions
Administer DARZALEX infusion intravenously at the infusion rate described below in Table 4. Consider incremental escalation of the infusion rate only in the absence of infusion reactions.
To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 4 below.

Table 4: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	Initial rate (first hour)	Rate increment[a]	Maximum rate
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 Day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

[b] Use a dilution volume of 500 mL for the 16 mg/kg dose only if there were no infusion reactions the previous week. Otherwise, use a dilution volume of 1000 mL.

[c] Use a modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) only if there were no infusion reactions during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

~~**Table 4: Infusion rates for DARZALEX administration**~~

	~~Dilution volume~~	~~Initial rate (first hour)~~	~~Rate increment[a]~~	~~Maximum rate~~
~~**First infusion**~~	~~1000 mL~~	~~50 mL/hour~~	~~50 mL/hour every hour~~	~~200 mL/hour~~
~~**Second infusion**[b]~~	~~500 mL~~	~~50 mL/hour~~	~~50 mL/hour every hour~~	~~200 mL/hour~~
~~**Subsequent infusions**[c]~~	~~500 mL~~	~~100 mL/hour~~	~~50 mL/hour every hour~~	~~200 mL/hour~~

~~[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.~~

~~[b] Use a dilution volume of 500 mL only if there were no infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.~~

~~[c] Use a modified initial rate for subsequent infusions (i.e. third infusion onwards) only if there were no infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.~~

For infusion reactions of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below *[see Infusion Reactions]*.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further

reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 4).

- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue DARZALEX treatment.

4.2.2 Recommended Concomitant Medications

Pre-infusion Medication

Administer the following pre-infusion medications to reduce the risk of infusion reactions to all patients 1-3 hours prior to every infusion of DARZALEX:

- Corticosteroid (long-acting or intermediate-acting)

Monotherapy:

Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).

Combination therapy:

Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX infusion *[Clinical Studies]*.

Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen-specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients receive dexamethasone (or equivalent) as a pre-medication.

- Antipyretics (oral acetaminophen 650 to 1000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion Medication

Administer post-infusion medication to reduce the risk of delayed infusion reactions to all patients as follows:

Monotherapy:

Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following all DARZALEX infusions (beginning the day after the infusion).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent, the day after the DARZALEX infusion.

However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed *[see Clinical Studies]*.

In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting DARZALEX and continue for 3 months following treatment *[see Undesirable effects]*.

4.2.3 Dose Modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of hematological toxicity *[see Neutropenia and Thrombocytopenia]*. For information concerning drugs given in combination with DARZALEX, see manufacturer's prescribing information.

4.2.4 Preparation for Administration

DARZALEX is for single use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient actual body weight.
- Check that the DARZALEX solution is colorless to pale yellow. Do not use if opaque particles, discoloration or other foreign particles are present.
- Remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection, USP as specified in Table 4 *[see Recommended Dose and Schedule]*. Infusion bags/containers must be made of either polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, administer the diluted solution immediately at room temperature 15°C–25°C (59°F–77°F) and in room light. Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time).
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2°C––8°C (36°F–46°F) and protected from light. Do not freeze.

4.2.5 Administration

- If stored in the refrigerator, allow the solution to come to room temperature. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP or PE.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.

4.2.6 Use in Specific Populations

4.2.6.1 Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

4.2.6.2 Geriatric Use

Of the 1166 patients that received DARZALEX at the recommended dose, 46% were 65 to 75 years of age, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies]*.

4.3 Contraindication

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Special warnings and precautions for use and Undesirable effects].*

~~None.~~

4.4 Special warnings and precautions for use

4.4.1 Infusion Reactions

DARZALEX can cause severe and/or serious infusion reactions including anaphylactic reactions. In clinical trials, approximately~~. Approximately~~ half of all patients experienced an infusion reaction.~~,~~ M~~m~~ost infusion reactions occurred during the first infusion and were Grade 1-2 *[see Undesirable effects]*.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Undesirable effects]*.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy ~~for~~ if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care~~s~~. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re~~-~~starting the infusion *[see Recommended Dose and Schedule]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Recommended Concomitant Medications]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

4.4.2 Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Effects of Daratumumab on Laboratory Tests]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

4.4.3 Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Undesirable effects]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

4.4.4 Thrombocytopenia

DARZALEX may increase thrombocytopenia induced by background therapy *[see Undesirable effects]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

4.4.5 Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein *[see Effects of Daratumumab on Laboratory Tests]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.~~other methods to evaluate the depth of response.~~

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or

other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

4.6.2 Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

4.6.3 Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

4.7 Effects on ability to drive and use machine

Not applicable.

4.8 Undesirable effects

The following clinically significant~~serious~~ adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Infusion Reactions]*.
- Neutropenia *[see Neutropenia]*.
- Thrombocytopenia *[see Thrombocytopenia]*.

4.8.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 1166 patients with multiple myeloma including 872 patients from three Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide and dexamethasone (DRd, n=283; POLLUX), bortezomib and dexamethasone (DVd, n=243; CASTOR) or bortezomib, melphalan

and prednisone (D-VMP, n=346; ALCYONE), and five open-label, clinical trials in which patients received DARZALEX either in combination with pomalidomide and dexamethasone (DPd, n=103; EQUULEUS), in combination with lenalidomide and dexamethasone (n=35), or as monotherapy (n=156).

Newly Diagnosed Multiple Myeloma

Combination Treatment with Bortezomib, Melphalan and Prednisone

Adverse reactions described in Table 5 reflect exposure to DARZALEX (D-VMP arm) for a median treatment duration of 14.7 months (range: 0 to 25.8 months) and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in ALCYONE. The most frequent adverse reactions (≥20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 45: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the D-VMP arm in ALCYONE

Body System Adverse Reaction	**D-VMP (N=346)**			**VMP (N=354)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	28	4	1	0	0	0
General disorders and administration site conditions						
Edema peripheral[b]	21	1	< 1	14	1	0
Infections and infestations						
Upper respiratory tract infection[c]	48	5	0	28	3	0
Pneumonia[d]	16	12	< 1	6	5	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[e]	16	< 1	0	8	< 1	0
Dyspnea[f]	13	2	1	5	1	0
Vascular disorders						
Hypertension[g]	10	4	< 1	3	2	0

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, bronchitis bacterial, epiglottitis, laryngitis, laryngitis bacterial, metapneumovirus infection, nasopharyngitis, oropharyngeal candidiasis, pharyngitis, pharyngitis streptococcal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, tracheitis, tracheobronchitis, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection.

[d] pneumonia, lung infection, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis

[e] cough, productive cough

[f] dyspnea, dyspnea exertional

[g] hypertension, blood pressure increased

Laboratory abnormalities worsening during treatment from baseline listed in Table 6.

Table 56: Treatment-emergent hematology laboratory abnormalities in ALCYONE

	D-VMP (N=346) %			VMP (N=354) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	47	18	0	50	21	0
Thrombocytopenia	88	27	11	88	26	16
Neutropenia	86	34	10	87	32	11
Lymphopenia	85	46	12	83	44	9

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide

Adverse reactions described in Table 7 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in POLLUX. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 67: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DRd arm in POLLUX

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 8.

Table 78: Treatment-emergent hematology laboratory abnormalities in POLLUX

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grades**	**Grade 3**	**Grade 4**
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 9 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in CASTOR. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 89: Adverse reactions reported in ≥10% of patients and with at least a 5% greater frequency in the DVd arm CASTOR

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, edema, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[d] cough, productive cough, allergic cough

[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 10.

Table 910: Treatment-emergent hematology laboratory abnormalities in CASTOR

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	< 1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Combination Treatment with Pomalidomide

Adverse reactions described in Table 11 reflect exposure to DARZALEX, pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in EQUULEUS. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms,

back pain, arthralgia, dizziness, insomnia, cough and dyspnea. The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients.

Table 10~~11~~: Adverse reactions with incidence ≥10% reported in EQUULEUS

Body System	**DPd (N=103)**		
Adverse Reaction	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	50	4	0
Gastrointestinal disorders			
Diarrhea	38	3	0
Constipation	33	0	0
Nausea	30	0	0
Vomiting	21	2	0
General disorders and administration site conditions			
Fatigue	50	10	0
Pyrexia	25	1	0
Chills	20	0	0
Edema peripheral[b]	17	4	0
Asthenia	15	0	0
Non-cardiac chest pain	15	0	0
Pain	11	0	0
Infections and infestations			
Upper respiratory tract infection[c]	50	4	1
Pneumonia[d]	15	8	2
Metabolism and nutrition disorders			
Hypokalemia	16	3	0
Hyperglycemia	13	5	1
Decreased appetite	11	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	26	1	0
Back pain	25	6	0
Arthralgia	22	2	0
Pain in extremity	15	0	0
Bone pain	13	4	0
Musculoskeletal chest pain	13	2	0
Nervous system disorders			
Dizziness	21	2	0
Tremor	19	3	0
Headache	17	0	0
Psychiatric disorders			
Insomnia	23	2	0
Anxiety	13	0	0

Table 1011: Adverse reactions with incidence ≥10% reported in EQUULEUS

Respiratory, thoracic and mediastinal disorders			
Cough[e]	43	1	0
Dyspnea[f]	33	6	1
Nasal congestion	16	0	0

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema, edema peripheral, peripheral swelling.

[c] acute tonsillitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection

[d] lung infection, pneumonia, pneumonia aspiration

[e] cough, productive cough, allergic cough

[f] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 12.

Table 1112: Treatment-emergent hematology laboratory abnormalities in EQUULEUS

	DPd (N=103) %		
	Any Grade	**Grade 3**	**Grade 4**
Anemia	57	30	0
Thrombocytopenia	75	10	10
Neutropenia	95	36	46
Lymphopenia	94	45	26

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 13. Table 14 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 12~~13~~: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

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

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 13~~14~~: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=1166) the incidence of any grade infusion reactions was 40% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2~~second~~ infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction at Week 2~~ with second~~ or subsequent infusions. Grade 4 infusion reactions were reported in 2/1166 (0.2%) of patients.

The median time to onset of a reaction was 1.4 hours (range: 0 to 72.8 hours). The incidence of infusion modification due to reactions was 37%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were 7.0, 4.3, and 3.4 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

In EQUULEUS, 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 infusion-related reactions was 42%, with 36% of patients experiencing infusion reactions 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.

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; D-VMP:23%, VMP:15%; DPd: 28%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively, 4% versus 3% of patients in the DVd and Vd groups respectively, 1% each in the D-VMP and VMP groups respectively, and in 5% of patients receiving DPd. Fatal infections were generally balanced between the DARZALEX containing regimens and active control arms (<2%) in the controlled studies and were primarily due to pneumonia and sepsis.

4.8.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to daratumumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 411 combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination

therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

4.8.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DARZALEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction

4.9 Overdose

Not applicable.

5. Pharmacological Properties

5.1 Mechanism of Action

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab.

5.2 Pharmacodynamic Properties

NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+$CD56^{dim}$) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment.

Cardiac Electrophysiology

DARZALEX as a large protein has a low likelihood of direct ion channel interactions. There is no evidence from non-clinical or clinical data to suggest that DARZALEX has the potential to delay ventricular repolarization.

5.3 Clinical Studies

5.3.1 Newly Diagnosed Multiple Myeloma

Combination Treatment with Bortezomib, Melphalan and Prednisone (VMP) in Patients Ineligible for Autologous Stem Cell Transplant

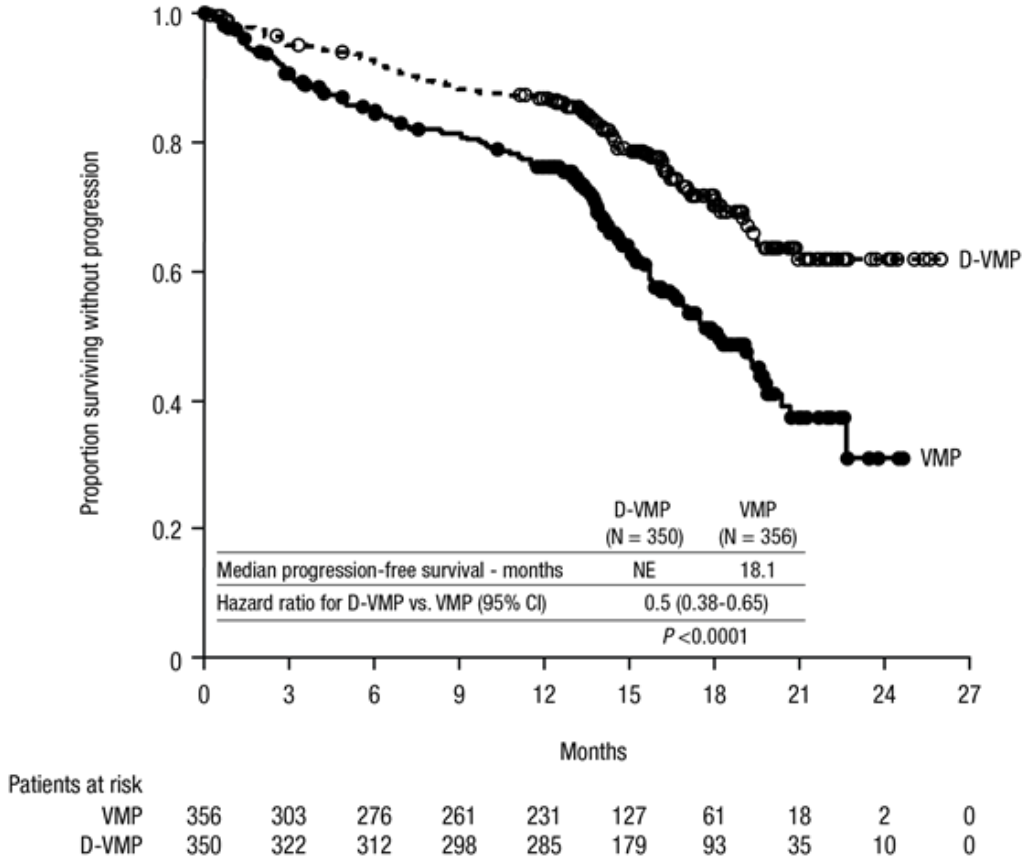
ALCYONE (NCT02198~~8~~5479), an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4

doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Nineteen percent of patients had ISS Stage I, 42% had ISS Stage II and 38% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

ALCYONE demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months (95% CI:16.53, 19.91) in the VMP arm (hazard ratio [HR]=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 1: Kaplan-Meier Curve of PFS in ALCYONE



Additional efficacy results from ALCYONE are presented in Table 15 below.

Table 1415: Additional efficacy results from ALCYONE

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) n(%)[a]	318 (90.9%)	263 (73.9%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	63 (18.0%)	25 (7.0%)
Complete response (CR)	86 (24.6%)	62 (17.4%)
Very good partial response (VGPR)	100 (28.6%)	90 (25.3%)
Partial response (PR)	69 (19.7%)	86 (24.2%)
MRD negativity rate[a, c] n(%)	78 (22.3%)	22 (6.2%)
95% CI (%)	(18.0, 27.0)	(3.9, 9.2)
p-value[d]	<0.0001	
MRD negativity rate in patients with CR or better[c] n(%)	74 (49.7%)	22 (25.3%)
95% CI (%)	(41.4, 58.0)	(16.6, 35.7)

D-VMP = daratumumab-bortezomib-melphalan-prednisone; VMP = bortezomib-melphalan-prednisone; MRD = minimal residual disease; CI = confidence interval

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[c] Based on threshold of 10^{-5}

[d] p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 0.5+, 23.7+) in the VMP group.

5.3.2 Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

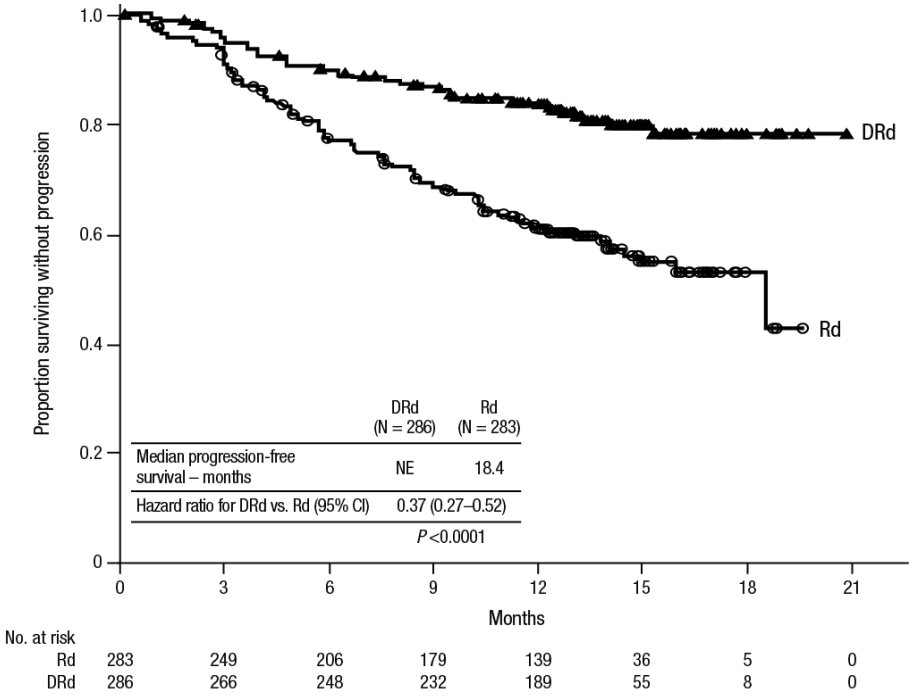
POLLUX (NCT02076009), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior PI, 55% of patients had received a prior immunomodulatory agent, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and immunomodulatory agent. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of

patients were refractory to a PI only, and 21% were refractory to bortezomib. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

POLLUX demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing 63% reduction in the risk of disease progression or death in patients treated with DRd.

Figure 2: Kaplan-Meier Curve of PFS in POLLUX



Additional efficacy results from POLLUX are presented in Table 16 below.

Table 1516: Additional efficacy results from POLLUX[a]

	DRd (n=286)	**Rd (n=283)**
Overall response (sCR+CR+VGPR+PR)	261 (91.3%)	211 (74.6%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	51 (17.8%)	20 (7.1%)
Complete response (CR)	70 (24.5%)	33 (11.7%)
Very good partial response (VGPR)	92 (32.2%)	69 (24.4%)
Partial response (PR)	48 (16.8%)	89 (31.4%)

DRd = daratumumab- lenalidomide-dexamethasone; Rd = lenalidomide-dexamethasone

[a] Based on Intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 1 month (range: 0.9 to 13 months) in the DRd group and 1.1 months (range: 0.9 to 10 months) in the Rd group. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group.

With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group.

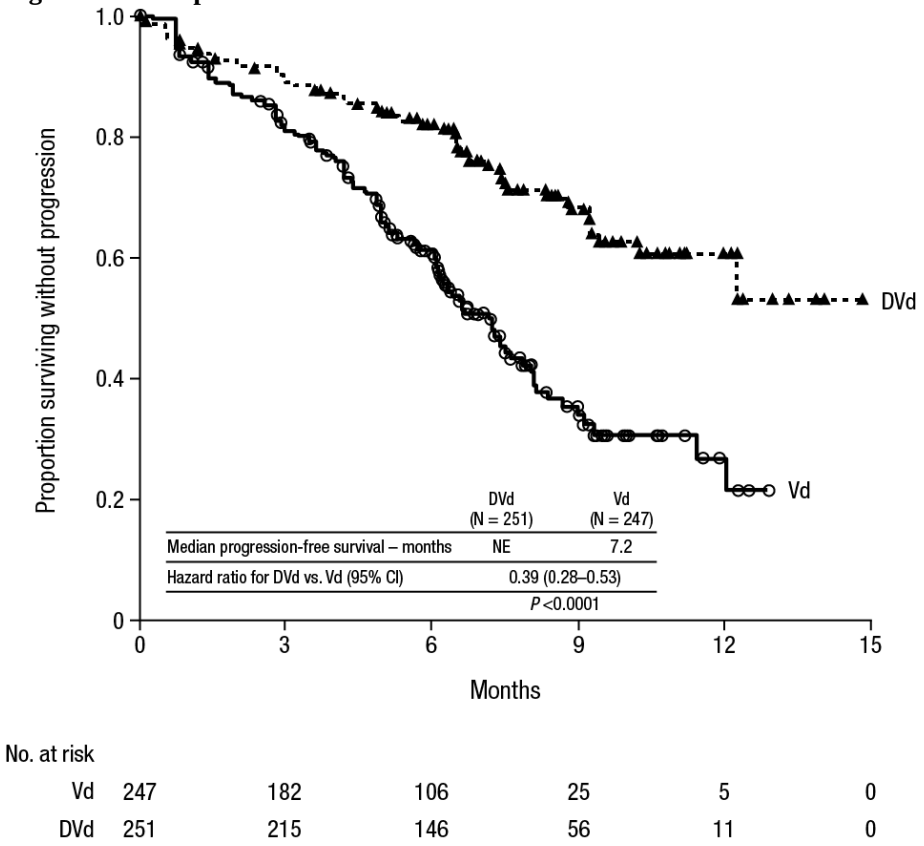
Combination Treatment with Bortezomib and Dexamethasone

CASTOR (NCT02136134), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion 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 infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas DARZALEX was given until disease progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were in general well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an immunomodulatory agent only, with 24% patients in the DVd arm and 33% of patients in the Vd arm respectively refractory to lenalidomide. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

CASTOR demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd.

Figure 3: Kaplan-Meier Curve of PFS in CASTOR



No. at risk

Vd	247	182	106	25	5	0
DVd	251	215	146	56	11	0

Additional efficacy results from CASTOR are presented in Table 17 below.

Table 1617: Additional efficacy results from CASTOR[a]

	DVd (n=251)	Vd (n=247)
Overall response (sCR+CR+VGPR+PR)	199 (79.3%)	148 (59.9%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	11 (4.4%)	5 (2.0%)
Complete response (CR)	35 (13.9%)	16 (6.5%)
Very good partial response (VGPR)	96 (38.2%)	47 (19.0%)
Partial response (PR)	57 (22.7%)	80 (32.4%)

DVd = daratumumab- bortezomib-dexamethasone; Vd = bortezomib-dexamethasone

[a] Based on Intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group.

With a median follow-up of 7.4 months, 65 deaths were observed; 29 in the DVd group and 36 in the Vd group were observed.

Combination Treatment with Pomalidomide and Dexamethasone

EQUULEUS (NCT01998971) was an open-label trial in which 103 patients with multiple myeloma who had received a prior PI and an immunomodulatory agent, received 16 mg/kg DARZALEX in combination with pomalidomide and low-dose dexamethasone until disease progression. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week]

cycles) was given with low dose oral or intravenous dexamethasone 40 mg/ week (reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.
The median patient age was 64 years (range: 35 to 86 years) with 8% of patients ≥75 years of age. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent (74%) of patients had received prior ASCT. Ninety-eight percent (98%) of patients received prior bortezomib treatment, and 33% of patients received prior carfilzomib. All patients received prior lenalidomide treatment, with 98% of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent (89%) of patients were refractory to lenalidomide and 71% refractory to bortezomib; 64% of patients were refractory to bortezomib and lenalidomide.
Efficacy results were based on overall response rate as determined by Independent Review Committee using IMWG criteria (see Table 18).

Table 1718: Efficacy results for EQUULEUS

	N=103
Overall response rate (ORR) 95% CI (%)	61 (59.2%) (49.1, 68.8)
Stringent complete response (sCR)	8 (7.8%)
Complete response (CR)	6 (5.8%)
Very good partial response (VGPR)	29 (28.2%)
Partial response (PR)	18 (17.5%)

ORR = sCR+CR+VGPR+PR
CI = Confidence Interval

The median time to response was 1 month (range: 0.9 to 2.8 months). The median duration of response was 13.6 months (range: 0.9+ to 14.6+ months).

Monotherapy
SIRIUS (NCT01985126), was an open-label trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. In 106 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression.
The median patient age was 63.5 years (range: 31 to 84 years), 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent, and 77% were refractory to alkylating agents.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 19).

Table 18~~19~~: Efficacy results for SIRIUS

	N=106
Overall response rate (ORR) 95% CI (%)	31 (29.2%) (20.8, 38.9)
Stringent complete response (sCR)	3 (2.8%)
Complete response (CR)	0
Very good partial response (VGPR)	10 (9.4%)
Partial response (PR)	18 (17.0%)

ORR = sCR+CR+VGPR+PR

CI = confidence interval

The median time to response was 1 month (range: 0.9 to 5.6 months). The median duration of response was 7.4 months (range: 1.2 to 13.1+ months).

Study GEN501 (NCT00574288) was an open-label dose escalation trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies. In 42 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression.

The median patient age was 64 years (range: 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% of patients were refractory to both, a PI and an immunomodulatory agent, and 60% of patients were refractory to alkylating agents.

Overall response rate was 36% (95% CI: 21.6, 52.0%) with 1 CR and 3 VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not estimable (range: 2.2 to 13.1+ months).

5.3.3 References

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

5.4 Pharmacokinetic properties

Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg of DARZALEX in combination with other treatments, increases in area under the concentration-time curve (AUC) were more than dose-proportional.

Following the recommended dose of 16 mg/kg when DARZALEX was administered as monotherapy or in combination therapy, the mean serum maximal concentration (C_{max}) value at the end of weekly dosing, was approximately 2.7 to 3-fold higher compared to the mean serum C_{max} following the first dose. The mean ± standard deviation (SD) trough serum concentration (C_{min}) at the end of weekly dosing was 573 ± 332 µg/mL when DARZALEX was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when DARZALEX was administered as combination therapy. Split dosing of the first dose resulted in a different PK profile in the first day compared to single dosing; however, similar C_{max} and C_{min} concentrations were both predicted and observed following the administration of the second split dose on Week 1 Day 2.

-When DARZALEX was administered as monotherapy, daratumumab steady state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean ± SD ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 ± 0.5.

Distribution

At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when DARZALEX was administered as monotherapy and 4.4 ± 1.5 L when DARZALEX was administered as combination therapy.

Elimination

Daratumumab clearance decreased with increasing dose and with multiple dosing. At the recommended dose of 16 mg/kg of DARZALEX as monotherapy, the mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day. The mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days when DARZALEX administered as monotherapy and a mean of 22-23 days when DARZALEX was administered as combination therapy.

Specific Populations

The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered DARZALEX as monotherapy or as combination therapy: sex, age (31 to 93 years), mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate aminotransaminase (AST)>ULN] and moderate (total bilirubin 1.5 to 3 times ULN and any AST) hepatic impairment, or renal impairment [Creatinine clearance (CLcr) 15 -89 mL/min]. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment is unknown. Increasing body weight increased the central volume of distribution and clearance of daratumumab, supporting the body weight-based dosing regimen.

Drug Interactions

Effect of Other Drugs on Daratumumab

The coadministration of lenalidomide, pomalidomide or bortezomib with DARZALEX did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

The coadministration of DARZALEX with bortezomib or pomalidomide did not affect the pharmacokinetics of bortezomib or pomalidomide.

5.5 Preclinical Safety data

5.5.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females.

6. Pharmaceutical Particulars

6.1 List of excipient

Glacial acetic acid, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride, and water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

See expiry date on the outer pack.

6.4 Special precautions for storage
Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
Do not freeze or shake. Protect from light. This product contains no preservative.
Keep out of the sight and reach of children.

6.5 Nature and contents of container
DARZALEX is a colorless to pale yellow, preservative-free solution for intravenous infusion supplied as:
5 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 100 mg of daratumumab. Pack size of 1 vial.
20 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 400 mg of daratumumab. Pack size of 1 vial.

Patient Counseling Information
Advise the patient to read the approved patient labeling (Patient Information).
Infusion Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:
- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Infusion Reactions and Undesirable effects]*.

Neutropenia
- Advise patients that if they have a fever, they should contact their healthcare professional *[see Neutropenia and Undesirable effects]*.

Thrombocytopenia
- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Thrombocytopenia and Effects of Daratumumab on Laboratory Tests]*.

Interference with Laboratory Tests
Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Interference with Serological Testing and Effects of Daratumumab on Laboratory Tests]*.
Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Interference with Determination of Complete Response and Effects of Daratumumab on Laboratory Tests]*.

7. Marketing Authorization Holder
See the end of the leaflet.

8. Marketing Authorization Numbers
See table below.

9. Date of authorization
See table below.

Manufactured by	**Market Authorization Number**	**Date of Authorization**
Cilag AG Schaffhausen, Switzerland	1C 30/60 (NBC)	3 August 2017

Manufactured by	Market Authorization Number	Date of Authorization
Vetter Pharma Fertigung GmbH & Co. KG Ravensburg, Germany	1C 31/60 (NBC)	3 August 2017

10. Date of revision of the text

FebMay 20198

Warning according to the announcement from ministry of public health

This medicinal product may cause serious harm. It must be used only under physician's supervision.

Imported by

Janssen-Cilag Ltd.
106 Moo 4 Lad Krabang Industrial Estate,
Chalongkrung Rd., Lamplatew, Lad Krabang,
Bangkok 10520
Tel: +662-792-7200
Fax: +662-792-7222