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:

ตารางที่ 1 สรุปรายงานการศึกษาวิจัยทางคลินิกของแต่ละข้อบ่งใช้

ข้อบ่งใช้	รายงานการศึกษาวิจัยทางคลินิก	ผลการศึกษาวิจัยทางคลินิก
1. 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	Study EQUULEUS (NCT01998971) Duration: 10 Mar 2014 - 16 Jun 2017, Synoptic CSR: 25 Sep 2017 An Open-label, Multicenter, Phase 1b Study of JNJ-54767414 (HuMax® CD38) (AntiCD38 Monoclonal Antibody) in Combination with Backbone Regimens for the Treatmentof Subjects with Dose regimen • *Daratumumab:* In the VMP+D regimen, daratumumabQW for 1 cycle, then Q3W for 8 cycles. • *Backbone regimen in scope for CSR:* *VMP+D:* VELCADE1.3mg/m2 on Days1,4,8,11, 22,25, 29; melphalan 9 mg/m2Days 1-4;dexamethasone 40 mg weekly (subjects 275 years) or 20mg (subjects >75 years), Daratumumab 16 mg/kg onDays 1, 8, 15, 22, 29, 36 Treatment group: VMP+D =12	ผลการศึกษาวิจัย • Daratumumab in combination with bortezomib, melphalan and prednisone demonstrated efficacy, with an overall response rate of 92% in subjects with newly diagnosed multiple myeloma who were unsuitable candidates for stem cell transplant. • Daratumumab in combination with VMP had a manageable safety profile consistent with the known safety profile of the individual components of the regimen. Based on these preliminary data, no new safety signals were identified. สรุปผล การใช้ยา Daratumumab ร่วมกับ VMP ใน patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant พบว่าให้ผลในการรักษาโรคดังกล่าวได้ ผู้ป่วยตอบสนองต่อการรักษา 92%
	Study ALCYONE (NCT02185479) Duration: 26 Jan 2015 - 12 Jun 2017, CSR 31 Oct 2017 A Phase 3, Randomized, Controlled, Open-label Study of VELCADE Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination with VMP (VMP+D), inSubjects with Previously Untreated Multiple Myeloma	ผลการศึกษาวิจัย: • A statistically significant 50% reduction in the risk of disease progression or death compared with VMP alone (HR=0.50; 95% confidence interval [CI]: 0.38, 0.65; p<0.0001). • The combination of daratumumab with VMP resulted in significantly

	who are Ineligible for High-dose Therapy Dose regimen • *Daratumumab solution (intravenous)* All cycles were 6 weeks. Cycle 1, Day 1 was the dayof the first full dose of daratumumab. Daratumumab (16 mg/kg) was administered at following dosing schedule: Cycle 1: Days 1, 8, 15, 22, 29 and 36 (weekly [QW]). Cycle 2 to 9: Days 1 and 22 (Q3W). Cycles 10+: Day 1 (every 4 weeks [Q4W]) • *Velcade* 1.3 mg/m2 SC on the following dosing schedule: Cycle 1: Days 1, 4, 8, 11, 22, 25, 29, and 32 Cycle 2 to 9: Days 1, 8, 22, and 29 • *Melphalan* 9 mg/m2 PO and prednisone PO 60 mg/m2on Days 1 to 4 of each Velcade cycle. For subjects randomized to Treatment Arm B, 20mgdexamethasone was substituted for the planned dose of*prednisone* on Day 1 of each cycle. Treatment group: VMP+D = 346 VMP = 354	higher ORR (91% versus 74%; odds ratio=3.55;p<0.0001), rate of VGPR or better (71% vs 50%; odds ratio=2.50; p<0.0001), and rate of CR of better(43% versus 24%; odds ratio=2.31; p<0.0001). The MRD negativity rate at the sensitivity threshold of 10^{-5} was more than tripled in subjects treated with VMP+D (22%) compared with subjects treated with VMP(6%) (odds ratio=4.36; p<0.0001). • Daratumumab in combination with VMP was well-tolerated, and did not result in any new safety signals. สรุปผล การใช้ยา Daratumumab ร่วมกับ VMP ใน patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant พบว่าให้ผลในการรักษาโรคดังกล่าวได้ และดีกว่าการใช้ VMP อย่างมีนัยสำคัญทางสถิติ
2. In combination with pomalidomide and	Study EQUULEUS (NCT01998971) An Open-label, Multicenter, Phase 1b Study of JNJ-54767414 (HuMax®	ผลการศึกษาวิจัย Study I

dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor	CD38) (Anti-CD38 Monoclonal Antibody) in Combination with Backbone Regimens for the Treatment of Subjects with Multiple Myeloma *The study has 2 planned data cutoff time points:* • Duration-1 (Study I): 10 Mar 2014 - 06 Feb 2015, Synoptic CSR: 4 May 2015 • Duration-2 (Study II): 10 Mar 2014 - 07 Mar 2016, Abbreviated CSR: 29 July 2016 *Number of Subjects:* Approximately 133 subjects (approximately 12 per VTd+D and VMP+D treatment regimen, 6 for the Vd+D treatment regimen, and 103 for the Pom-dex treatment regimen) are to be enrolled in this study. *Study I* At the time of this analysis, 49 subjects were treated, and their data are included in this synoptic CSR. Vd+D= 6, VTd+D=11, VMP+D= 8, Pom-dex+D= 24 *Study II* *Vd+D= 6, VTd+D= 12, VMP+D= 12, DpD= 103* Dose regimen • Daratumumab: In the Vd, VTd, and VMP regimens, daratumumab was to be administered qw as an IV infusion for 6 wks (equivalent to 2x Vd/VTd cycles and 1x VMP cycle). Subsequently, daratumumab was to be administered q3w in combination with the applicable backbone treatment	• The safety profile of daratumumab in combination with Vd, VTd, VMP, and Pom-dex was consistent with that of the observed safety profile of the backbone treatment regimens with the exception of IRR a known toxicity of daratumumab; no additive toxicities were observed with the addition of daratumumab. • IRRs were reported in 49% of subjects and were generally mild, no grade 4 IRR was reported. The vast majority of IRRs occurred during the first 2 infusions; and most subjects who experienced an IRR were able to continue full-dose of therapy with supportive treatment. IRRs did not result in hospitalization or discontinuation of treatment. <u>Study II</u> • Daratumumab in combination with pomalidomide and dexamethasone demonstrated compelling efficacy with an overall response rate of 59% • Adding daratumumab to Pomalidomide-Dexamethasone leads to higher and deeper responses, with longer PFS, compared with historical data of a similar population of patients treated with Pomalidomide-Dexamethasone alone • DpD regimen had a manageable safety profile consistent with the known safety profile of the individual components of the regimen.

	regimen. In the Pomalidomide-Dexamethasone regimen, daratumumab was to be administered qw for 2 cycles, then q2w for 4 cycles, and thereafter q4w. • Backbone Regimens: In the Vd and VTd regimens, subjects were to receive 1.3 mg/m2 VELCADE as an SC injection twice a week for four 21-day cycles, followed by qw injections for the subsequent 14 cycles or until transplant; dexamethasone 20 mg was to be administered on the day of and the day after administration of VELCADE or daratumumab; thalidomide 100 mg was to be administered PO daily for 21 days. In the VMP regimen, subjects will receive 1.3 mg/m2 VELCADE as an SC injection twice a week for one 6- week cycle, followed by qw for subsequent cycles; melphalan was to be administered PO at 9 mg/m2, and prednisone was to be administered at 60 mg/m2 on Days 1 to 4 of each cycle. In the Pomalidomide-Dexamethasone regimen, pomalidomide 4 mg/day was to be administered PO once daily on Days 1 to 21 days of a 28-day cycle. Dexamethasone was to be administered at 40 mg (subjects ≤dministered at 40 mg (subjects) per week. For the maximal allowed treatment duration or until disease progression, unacceptable toxicity, or discontinuation of study treatment	*Pharmacokinetic, immunogenicity and biomarker results for Vd+D, VTd+D, VMP+D regimen.* • Daratumumab trough and Cmax serum concentrations were similar across treatment groups and comparable to that observed in prior studies, indicating combination with Vd+D, VTd+D, VMP+D or D-Pom-dex does not appear to alter the pharmacokinetics of daratumumab. • In addition, analysis of the pharmacokinetic profiles of bortezomib, pomalidomide, and thalidomide indicate there is no clinically relevant impact of daratumumab on the pharmacokinetics of these molecules. • Only 1.6%was positive for anti-daratumumab antibodies, indicating a low risk of immunogenicity, as previously reported in monotherapy studies <u>สรุปผล</u> การใช้ยา Daratumumab ร่วมกับ Pomalidomide-Dexamethasone ใน patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor พบว่าให้ผลในการรักษาโรคดังกล่าวได้ ผู้ป่วยตอบสนองต่อการรักษา 59% ในด้านความปลอดภัยไม่พบผลข้างเคียงที่เพิ่มขึ้นที่เกิดจากยา Daratumumab

CR	=	Complete Response
DpD	=	Pomalidomide-Dexamethasone-Daratumumab
VMP+D	=	Daratumumab-Velcade-Melphalan-Prednisone
IRR	=	Infusion-Related Reaction
MRD	=	Minimal residual disease
ORR	=	Overall Response Rate
PFS	=	Progression-Free Survival
QW	=	every week; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks
Vd	=	Velcade-Dexamethasone
Vd+D	=	Velcade-Dexamethasone-Daratumumab
VMP	=	Velcade-Melphalan-Prednisone
VTd	=	Velcade-Thalidomide-Dexamethasone
VTd+D	=	Velcade-Thalidomide-Dexamethasone-Daratumumab
Velcade	=	Bortezomib
VGPR	=	Very Good Partial Respons