Public Assessment Report

DARZALEX FASPRO (INITIAL)

INFORMASI PRODUK

Nama Obat	:	Darzalex Faspro
Zat Aktif	:	Tiap vial mengandung: Daratumumab 1800 mg
Bentuk Sediaan	:	Larutan injeksi
Kemasan	:	Dus, 1 vial @ 15 ml
Pendaftar	:	PT. Integrated Healthcare Indonesia, Jakarta
Produsen	:	Cilag AG, Schaffhausen, Switzerland
Kategori Registrasi	:	Produk Biologi Baru
Indikasi yang diajukan:	:	*Multiple Myeloma* *DARZALEX FASPRO is indicated:* ● *DARZALEX FASPRO is indicated 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.* ● *DARZALEX FASPRO is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.* ● *DARZALEX FASPRO is indicated in combination with lenalidomide and dexamethasone, or bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.* *AL Amyloidosis* *DARZALEX FASPRO is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.*
Posologi yang diajukan	:	*DARZALEX FASPRO subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified.* *DARZALEX FASPRO should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.* *It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed.* *For patients currently receiving daratumamab intravenous formulation, DARZALEX FASPRO solution for subcutaneous injection may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose. Pre- and post-injection medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below "Recommended concomitant medicinal products" and section Special warnings and precautions for use.* *Posology* *Multiple Myeloma* *Dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle regimen) and for monotherapy* *The recommended dose is 1800 mg of DARZALEX FASPRO solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 1.*

Table 1: DARZALEX FASPRO® dosing schedule in combination with lenalidomide and dexamethasone (Rd) (4-week cycle dosing regimen) and monotherapy

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.

Dexamethasone should be administered at 40 mg/week (or a reduced dose of 20 mg/week for patients > 75 years).
For dose and schedule of medicinal products administered with DARZALEX FASPRO solution for subcutaneous injection, see section Pharmacodynamic properties and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)
The recommended dose is 1800 mg of DARZALEX FASPRO solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 2.

Table 2: DARZALEX FASPRO® 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.

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by once weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX FASPRO solution for subcutaneous injection, see section Pharmacodynamic properties.

Dosing schedule in combination with bortezomib (3-week cycle regimen)
The recommended dose is 1800 mg of DARZALEX FASPRO solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 3.

Table 3: DARZALEX FASPRO® dosing schedule in combination with bortezomib and dexamethasone (Vd) (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.

Dexamethasone should be administered at 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 bortezomib treatment cycles or a reduced dose of 20 mg/week for patients > 75 years, underweight (BMI < 18.5), poorly controlled diabetes mellitus or prior intolerance to steroid therapy.
For dose and schedule of medicinal products administered with DARZALEX FASPRO solution for subcutaneous injection, see section Pharmacodynamic properties and the corresponding Summary of Product Characteristics.

AL Amyloidosis
Dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle regimens)
The recommended dose is 1800 mg of DARZALEX FASPRO solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 4.

Table 4: DARZALEX FASPRO® dosing schedule for AL amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone ([VCd];4-week cycle dosing regimen)[a]

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

[a] In the clinical study, DARZALEX FASPRO® was given until disease progression or a maximum of 24 cycles (~ 2 years) from the first dose of study treatment.
[b] First dose of the every-2-week dosing schedule is given at week 9.
[c] First dose of the every-4-week dosing schedule is given at week 25.

For dose and schedule of medicinal products administered with DARZALEX

FASPRO solution for subcutaneous injection, see section Pharmacodynamic properties and the corresponding Summary of Product Characteristics.

Missed dose
If a planned dose of DARZALEX FASPRO is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications
No dose reductions of DARZALEX FASPRO are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section Special warnings and precautions for use). For information concerning medicinal products given in combination with DARZALEX FASPRO, see corresponding Summary of Product Characteristics. In clinical studies, no modification to rate or dose of DARZALEX FASPRO solution for subcutaneous injection was required to manage IRRs.

<u>Recommended concomitant medicinal products</u>
Pre-injection medicinal product
Pre-injection medicinal products (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of DARZALEX FASPRO solution for subcutaneous injection as follows:

- *Corticosteroid (long-acting or intermediate-acting)*
  - *Monotherapy:*
    Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg.
  - *Combination therapy:*
    Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX FASPRO solution for subcutaneous injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection medicinal product on DARZALEX FASPRO administration days (see section Pharmacodynamic properties). Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX FASPRO administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product.
- *Antipyretics (paracetamol 650 to 1 000 mg).*
- *Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).*

Post-injection medication
Administer post-injection medication to reduce the risk of delayed IRRs 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 FASPRO injections (beginning the day after the injection).
- *Combination therapy:*
  Consider administering low-dose oral methylprednisolone (?20 mg) or equivalent the day after the DARZALEX FASPRO injection. However, if a background regimen specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX FASPRO injection, additional post-injection medicinal products may not be needed (see section Pharmacodynamic properties).

If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any
background regimen corticosteroids) may be discontinued.
Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs,

these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation
Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations
Renal impairment
No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section Pharmacokinetic properties).

Hepatic impairment
No formal studies of daratumumab in patients with hepatic impairment have been conducted. No dosage adjustments are necessary for patients with hepatic impairment (see section Pharmacokinetic properties).

Elderly
No dose adjustments are considered necessary (see section Pharmacokinetic properties).

Paediatric population
The safety and efficacy of DARZALEX FASPRO in children aged below 18 years of age have not been established. No data are available (see section Pharmacodynamic properties).

Body weight (>120 kg)
Limited number of patients with body weight >120 kg have been studied using flat-dose (1 800 mg) DARZALEX FASPRO solution for subcutaneous injection and efficacy in these patients has not been established. No dose adjustment based on body weight can currently be recommended (see sections Special warnings and precautions for use and Pharmacokinetic properties).

Method of administration
DARZALEX FASPRO subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section Special precautions for disposal and other handling prior to administration.
To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.
Inject 15 mL DARZALEX FASPRO solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX FASPRO solution for subcutaneous injection at other sites of the body as no data are available.
Injection sites should be rotated for successive injections.
DARZALEX FASPRO solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.
Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the
injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
During treatment with DARZALEX FASPRO solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX FASPRO.

PENGANTAR

Darzalex Faspro merupakan produk biologi dengan zat aktif daratumumab. Saat ini, produk dengan zat aktif yang sama telah terdaftar di Indonesia oleh pendaftar yang sama dengan nama Darzalex. Perbedaan Darzalex dengan Darzalex Faspro adalah pada formulasi dan rute pemberian. Pada formulasinya Darzalex Faspro ditambahkan *Recombinant Human Hyaluronidase* (rHuPH20) sebuah peningkat permeabilitas. Darzalex diberikan melalui Intravena sedangkan Darzalex Faspro melalui Subkutan. Tujuan rute pemberian Subkutan adalah:

- memberikan kemudahan dalam pemberian produk obat
- mengurangi secara signifikan lama waktu pemberian obat dibandingkan dengan pemberian secara intravena
- mengurangi efek samping *infusion-related reactions* (IRRs).

Darzalex yang telah disetujui digunakan untuk pengobatan *multiple myeloma* secara intravena, sedangkan bentuk sediaan baru yang diajukan digunakan untuk pengobatan *multiple myeloma* dan *amyloidosis* secara subkutan.

ASPEK MUTU

Darzalex Faspro terdaftar dengan bentuk sediaan larutan injeksi. Zat tambahan yang digunakan adalah Sorbitol 735, 1 mg, Recombinant Human Hyaluronidase 30000 U, L-Histidine 4,9 mg, L-Histidine Monohydrochloride Monohydrate 18,4 mg, L-Methionine 13,5 mg , Polysorbate 20 6,0 mg, Water For Injection q.s. Darzalex Faspro dikemas dalam vial dengan 1 besar kemasan, yaitu Dus, 1 vial dengan volume isi 15 mL. Obat ini harus disimpan pada suhu dingin (2-8°C). Darzalex Faspro mengandung zat aktif daratumumab, sehingga aspek mutu zat aktif mengacu pada Darzalex.

Obat Jadi

Darzalex Faspro diproduksi, diuji, dan dirilis oleh Cilag AG, Schaffhausen, Switzerland Proses produksi dari Formulasi sampai dengan Pengemasan dilakukan di fasilitas Cilag AG, Schaffhausen, Switzerland. Pengujian obat juga dilakukan di Janssen Sciences Ireland UC dan di Janssen Biologics B.V., Netherlands.C Proses produksi secara umum terdiri atas *thawing and holding, compounding, pre-filtration, sterile filtration, aseptic filling, stoppering and capping, optical inspection, secondary packaging, dan other possible post-fill process steps (e.g., 100% container closure integrity test)*, Uraian proses produksi diserahkan dengan rincian dan memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan. Validasi terhadap proses produksi telah dilakukan, mencakup proses formulasi, fill finish dan validasi media fill. Hasil validasi menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan. Spesifikasi obat jadi telah ditetapkan, mencakup parameter uji, referensi metode uji serta kriteria penerimaannya. Prosedur uji telah divalidasi. Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang, variabilitas proses produksi maupun metode analisis dan data pengembangan proses yang relevant. Data stabilitas Produk jadi Darzalex Faspro mendukung penyimpanan obat jadi selama 24 bulan pada kondisi penyimpanan yang direkomendasikan yaitu 2°C - 8°C.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Studi non klinik Darzalex Faspro sama dengan studi non klinik Darzalex yang telah dievaluasi sebelumnya.

Studi Klinik

1. Untuk mendukung registrasi Darzalex Faspro, diserahkan 4 studi klinik untuk indikasi *multiple myeloma* [studi fase 1 (MMY1008), studi fase 1b (MMY1004), studi fase 2 (MMY2040), dan studi fase 3 (MMY3012)]; dan 1 studi klinik fase 3 (studi AMY3001) untuk indikasi *amyloid light-chain (AL) amyloidosis*.

2. Indikasi *multiple myeloma*
   a. Pada studi MMY1008, yang merupakan studi pada subjek Jepang dengan *relapsed or refractory multiple myeloma* (n=6), pemberian daratumumab subkutan (SC) 1800 mg menunjukkan hasil:
      1) Nilai ORR berdasarkan kriteria International Myeloma Working Group/IMWG (sCR+CR+VGPR+PR) adalah 66,7%, dimana 16,7% mencapai CR dan VGPR, 33,3% mencapai PR, 33,3% mencapai MR.
      2) *Median time to best response* yaitu 1,92 bulan (0,9-7,4 bulan).
      3) Berdasarkan *duration of response*, 25% (1 dari 4 subjek) mengalami PD yang terkonfirmasi setelah PR.
      4) Secara umum, keamanan pemberian injeksi Daratumumbab 1800 mg SC dapat ditoleransi.
   b. Studi MMY1004 (n= 78), yang mengevaluasi pemberian SC formulasi *mixed and delivery daratumumab* dan *recombinant human hyaluronidase/rHuPH20* (Dara-MD); dan *co-formulated daratumumab* dengan rHuPH20 (Dara-CF), menunjukkan hasil:
      1) Respon klinik terbaik ditunjukkan dengan 4 subjek (9%) pada kelompok Dara-MD mencapai sCR.
      2) Nilai ORR tampak sebanding antara kelompok Dara-MD 1800 mg dan Dara-CF 1800mg (42% vs 52%).

3) *Median duration of response* yaitu 6,4 bulan di kelompok Dara-MD 1200 mg dan 14,2 bulan di kelompok Dara-MD 1800 mg.
4) Berdasarkan estimasi Kaplan-Meier, sebanyak 50% subjek pada kelompok Dara-MD 1200 mg dan 89% subjek pada kelompok Dara-MD 1800 mg menunjukkan *progression-free* dan bertahan hidup hingga 6 bulan.
5) *Median time to response* lebih panjang pada kelompok Dara-MD 1200 mg (3,4 bulan) dibandingkan Dara-MD 1800 mg (1,9 bulan) dan Dara-CF 1800 mg (1 bulan).
6) Secara umum, profil keamanan pemberian Dara-MD dan Dara-CF dapat ditoleransi dengan baik.

c. Studi MMY2040 (n=199) yang bertujuan untuk mengevaluasi pemberian daratumumab SC dengan kombinasi regimen standar *multiple myeloma* pada subjek dengan *multiple myeloma*, menunjukkan bahwa kombinasi daratumumab SC memiliki efikasi dan keamanan yang baik:
1) ORR: 88,1% (90%CI: 79,5%, 93,9%) untuk kombinasi Daratumumab-Velcade-Melphalan-Prednisone (D-VMP)
2) ORR: 90,8% (90%CI: 82,6%, 95,9%) untuk kombinasi Daratumumab-Revlimid-Dexamethasone (D-Rd)
3) VGPR or better rate: 71,6% (95% CI: 61,2%, 80,6%) untuk kombinasi Daratumumab-Velcade-Revlimid-Dexamethasone (D-VRd)
4) Pemberian daratumumab SC dengan kombinasi lenalidomide dan dexamethasone, atau bortezomib, melphalan dan prednisone dapat ditoleransi dengan baik.

d. Studi No. MMY3012 merupakan studi fase 3 untuk menunjukkan bahwa daratumumab SC yang *co-formulated* dengan rHuPH20 non-inferior terhadap daratumumab IV berdasarkan parameter Overall Response Rate (ORR):
1) Nilai ORR kelompok daratumumab SC dibandingkan kelompok daratumumab IV, berturut-turut 41,1% dan 37,1%, dengan *Risk Ratio* 1,11 (CI 95%: 0,89, 1,37) sehingga memenuhi kriteria *non-inferiority*.
2) Profil keamanan relatif sebanding antara daratumumab SC dan IV kecuali dalam hal neutropenia (daratumumab SC 19,2% vs daratumumab IV 13,6%), dyspnea (daratumumab SC 5,4% vs daratumumab IV 10,9%) dan chills (daratumumab SC 5,8% vs daratumumab IV 12,4%).

3. Indikasi *amyloid light-chain (AL) amyloidosis*

a. Indikasi ini didukung oleh studi AMY3001 yang merupakan studi untuk mengevaluasi efikasi daratumumab SC + CyBorD dibandingkan CyBorD Tunggal pada pasien *newly diagnosed AL amyloidosis* (n=388).

b. Hasil studi menunjukkan:
1) *Overall CHR rate* menunjukkan perbedaan bermakna secara klinis antara kelompok daratumumab SC + CyBorD vs CyBorD tunggal (53,3% vs 18,1%, odds ratio=5,13; 95%CI: 3,22, 8,16, p <0,0001).
2) Profil keamanan daratumumab SC + CyBorD dapat ditoleransi pada subjek dengan *newly diagnosed AL amyloidosis*. TEAE dengan kejadian NLT 5% yang paling sering dilaporkan pada kelompok SC+CyBorD dibandingkan kelompok CyBorD yaitu diare, konstipasi, *peripheral sensory neuropathy, thrombocytopenia,* batuk, *asthenia, back pain, arthralgia*, dan infeksi saluran pernapasan atas. TEAE *grade* 3 atau 4 dengan kejadian NLT 5% yang paling sering dilaporkan pada kelompok SC+CyBorD yaitu *lymphonia, pneumonia, diarrhea, neutropenia, syncope,* dan *cardiac failure*. Tidak ada TEAE yang menyebabkan penghentian penggunaan obat terapi.

KEPUTUSAN

Mempertimbangkan data mutu, khasiat dan keamanan tersebut di atas, diputuskan registrasi baru Darzalex Faspro Larutan Injeksi **dapat diterima sesuai dengan indikasi dan posologi yang diajukan.**

Indikasi

Multiple Myeloma

DARZALEX FASPRO is indicated:

- *DARZALEX FASPRO is indicated 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.*
- *DARZALEX FASPRO is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.*
- *DARZALEX FASPRO is indicated in combination with lenalidomide and dexamethasone, or bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.*

AL Amyloidosis

DARZALEX FASPRO is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.