Public Assessment Report

ONCASPAR

INFORMASI PRODUK

Nama obat	:	Oncaspar
Bentuk sediaan	:	Serbuk Injeksi
Zat aktif	:	Pegaspargase 750 u/mL
Kemasan	:	Dus, 1 vial @ 3.750 unit
Pendaftar	:	PT Genero Pharmaceuticals
Produsen	:	Lyophilization Services of New England Inc, Gidy, France dikemas oleh Exeled Inc, USA dirilis oleh Les Laboratoires Servier Industrie, France
Kategori Registrasi	:	Variasi Major (Perubahan Posologi)
Indikasi yang diajukan:	:	*Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.*
Posologi yang diajukan	:	*Oncaspar should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored for any adverse reactions throughout the administration period (see section "Special warnings and precautions for use").*

<u>Posology:</u>
Oncaspar is usually administered as part of combination chemotherapy protocols with other antineoplastic agents (see also section "Interaction with other medicinal products and other forms of interaction").

<u>Recommended premedication:</u>
Premedicate patients with paracetamol, an H-1 receptor blocker (e.g. diphenhydramine), and an H-2 receptor blocker (e.g. famotidine) 30-60 minutes prior to administration of Oncaspar to decrease the risk and severity of both infusion and hypersensitivity reactions (see section "Special warnings and precautions for use").

<u>Paediatric patients and adults ≤21 years:</u>
The recommended dose in patients with a body surface area (BSA) ≥ 0.6 m^2 and who are ≤21 years of age is 2,500 U of pegaspargase (equivalent to 3.3 ml Oncaspar)/m2 body surface area every 14 days.
Children with a body surface area <0.6 m^2 should receive 82.5 U of pegaspargase (equivalent to 0.1 ml Oncaspar)/kg body weight every 14 days.

<u>Adults >21 years:</u>
Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2,000 U of pegaspargase (equivalent to 2.67 ml Oncaspar)/m^2 body surface area every 14 days.
Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of pegaspargase. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section "Special warnings and precautions for use").

Special populations
Renal impairment
As pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no dose adjustment is necessary in patients with renal impairment.
Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.
Elderly
There are limited data available for patients older than 65 years.

Method of administration
Oncaspar can be given by intramuscular (IM) injection or intravenous (IV) infusion.
For smaller volumes, the preferred route of administration is intramuscular. When Oncaspar is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If a higher volume is given, the dose should be divided and given at several injection sites.
Intravenous infusion of Oncaspar is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution.
The diluted solution can be given together with an already-running infusion of either sodium chloride 9 mg/ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of Oncaspar.
For instructions on reconstitution and dilution of this medicinal product before administration, see section 6.6 "Special precautions for disposal and other handling".

PENGANTAR
Oncaspar merupakan produk biologi dengan zat aktif Pegaspargase yang telah terdaftar, saat ini diajukan perubahan posologi berupa penambahan premedikasi. Latar belakang penambahan premedikasi ini adalah untuk mengurangi risiko dan keparahan reaksi hipersensitivitas yang muncul setelah pemberian obat, karena reaksi hipersensitivitas adalah efek samping yang sangat umum terjadi setelah pemberian Oncaspar. Selain itu juga ada permintaan dari FDA untuk melakukan review terhadap literatur serta guideline terkini yang mendukung pemberian premedikasi sebelum pemberian Oncaspar.

ASPEK MUTU
Tidak ada aspek mutu yang dievaluasi pada pengajuan registrasi variasi ini.

ASPEK KHASIAT DAN KEAMANAN
Untuk mendukung klim posology yang diajukan, diserahkan jurnal terpublikasi yang mendukung perubahan posology Oncaspar yang diajukan, yaitu pemberian premedikasi berupa paracetamol, H-1 receptor blocker (diphenhydramine) dan H-2 receptor blocker (famotidine) pada 30-60 menit sebelum pemberian Oncaspar sebagai berikut :

Publication reference	Premedication (type and dosage)	Population and participants analysed	Impact of premedication on AE/hypersensitivity	Comments
Advani, 2021	Corticosteroids, paracetamol, and diphenhydramine only in the CALGB 10403, dosage unknown	AYA (18-39) CALGB 10403: N=289 COG AALL0232: N=149	CALGB - Grade 3 to 4 hypersensitivity reactions declined from 10% to 4%. COG AALL0232 group no premedication: higher rates of hypersensitivity reactions requiring discontinuation of pegaspargase (14.6% grade 3/4)	In CALGB Premedication was introduced with amendment, leading to decline in the hypersensitivity compared to not premedicated.
Cooper, 2019	Diphenhydramine (1 mg/kg, max 50 mg/dose) &famotidine (1 mg/kg/dose, max 20 mg) or ranitidine (2 mg/kg/dose, max 150mg). For rechallenged, hydrocortisone (1 mg/kg, max 100 mg/dose)	Children, AYA 122 pts without premed. 68 pts with premed	AE rate: 17.2 vs 5.9 % Grade 4: 15 vs 0% (9 pts premedicated to prevent 1 event)	Since 2016: set up of a systematic premedication

Losasso, 2019	Paracetamol (10-15mg/kg). Diphenhydramine (1 mg/kg), corticosteroid (Methylprednisolone - 1 mg/kg)	Children, AYA (up to 30 yo) N=99 patients for main analysis N=46patients-subgroup for PK analysis	The incidence of grade 3 or 4 allergic reactions was 3.7% per dose with premedication versus 5.2% without. These values are not statistically significant (power 0,54). Premedication did not affect pegaspargase activity.	Additional finding - statistically significantly greater pegaspargase activity oftheday6–8 pegaspargase level with the use of premedication.
Marini, 2019	Paracetamol 15 mg/kg (max 650 mg) PO Diphenhydramine 1 mg/kg (max 50 mg) IV Hydrocortisone1 mg/kg (max 100 mg) IV Ondansetron0.15 mg/kg (max 8 mg) IV/PO Infusion rate: 10% over the 1st hour, 90% over 2nd hour (total infusion= 2 hours)	Children (COG protocols), AYA ALL PH- (CALGB 10403 (Alliance) protocol), Adults Ph- ALL up 65 yo (CALGB 9511 protocol or the USC/Douer regimen) N= 297 with PEG-asparaginase (163 pre-implementation and 134 post implementation).	This approach reduced the PEG- asparaginase to Erwinia switch rate, all measures confounded, from 21% (35 of 163) to 7% (10 of 134) (p=0.0035). Allergy Review Committee (MAARC) formation, guidance on how to manage hypersensitivity reactions	

Jurnal terpublikasi

1. *Advani, 2021*
   Comparison of CALGB 10403 (Alliance) and COG AALL0232 toxicity results in young adults with acute lymphoblastic leukemia.
   Sebanyak 318 pasien remaja – dewasa muda (usia 18-39 tahun) dengan diagnosis B atau T-cell precusor *acute lymphoblastic leukemia* direkrut dalam studi CALGB 10403 antara November 2007 sampai 2012 dan 158 pasien dari studi lain COG AALL0232 (mayoritas usia 16-21 tahun sebagian kecil 22-30 tahun) yang menerima pengobatan dengan prednisone dan kombinasi metotrexat/pegaspargase. Hasil studi menunjukan bahwa terjadi penurunan kejadian reaksi hipersensitivitas grade 3-4 pada protokol COG AALL0232 dibandingkan protokol CALGB 10403 dengan penambahan premedikasi kortikosteroid, asetaminofen, dan difenhidramin.

2. *Cooper, 2019*
   Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions.
   Penelitian dilakukan dengan melakukan review retrospektif terhadap pasien yang menerima asparaginase sebelum dan setelah premedikasi universal sebelum diberikan pegaspargase (PEG), dengan uji serum asparaginase activity (SAA) yang dilakukan 1 minggu setelahnya. pasien yang mengalami efek samping non alergi dieksklusi. *Primary end point* adalah substitusi ke Asparginase Erwinia chrysanthemi (ERW). *Secondary endpoint* mencakup AEs, pengujian SAA dan biaya. Asparginase Erwinia chrysanthemi (ERW) disetujui untuk hipersensitivitas terhadap PEG, tetapi kurang nyaman, lebih mahal dan menghasilkan aktivitas serum asparaginase (*serum asparaginase activity*/ SAA) yg lebih rendah.
   Hasil studi menunjukkan bahwa pemberian premedikasi diphenhydramine (1 mg/kg, maksimum 50 mg/dosis, IV atau oral) menurunkan reaksi hipersensitivitas klinis yang memerlukan substitusi obat dibandingkan pasien tanpa premedikasi (7,4% vs 17,2%; RR 0,427; 95% CI 0.27–0.69; P = 0,028) dan menurunkan *acute adverse events* (5,9% vs 17,2%; RR=0,342; 95% CI 0.2–0.58; P = 0,017).

3. *Losasso 2019*
   Retrospective cohort study monitoring PEG-asparaginase activity in acute lymphoblastic leukemia patients with and without premedication.
   Penelitian ini untuk melihat aktivitas asparaginase setelah pemberian pegaspargase (2500 unit/m^2) pada anak dan dewasa muda yang baru didiagnosis dengan ALL sel B dan T dari Desember 2013 hingga September 2016 (N=99). Data dari seluruh pasien (99 orang) digunakan untuk mengestimasi insidensi reaksi alergi grade 3 dan 4 berdasarkan pasien dan dosis. Untuk analisis farmakokinetik yang detail, digunakan subgrup semua pasien dari Mei 2014 – September 2016 (N=46) yang memiliki level pegaspargase terukur.
   Hasil studi menunjukkan bahwa pada pasien yang menerima premedikasi acetaminophen
   10–15 mg/kg orally, diphenhydramine 1 mg/kg orally or intravenously, dan methylprednisolone 1 mg/kg intravenously) 1 jam sebelum pemberian peg asparaginase, kejadian reaksi alergi grade 3-4 lebih rendah dibandingkan pasien tanpa premedikasi (3,7% vs 5,2%).

4. *Marini, 2019*
   A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage
   Periode penelitian tahun 2012-2018. 297 pasien diobati dengan peg asparaginase (163 pra-implementasi dan 134 pasca implementasi). Sebanyak 732 dosis peg asparaginase diberikan selama periode penelitian

(398 pra-implementasi dan 334 pasca implementasi). Sebelum implementasi, Erwinia digantikan pada 35 dari 163 (21%) pasien yang menerima peg asparaginase. Multidisciplinary asparagaginase allergy committee (MAARC) mengurangi tingkat peralihan dari 21% menjadi 7% dengan hanya 10 dari 134 pasien yang beralih ke Erwinia selama periode 2 tahun.
Hasil studi menunjukan bahwa pemberian premedikasi (acetaminophen 15 mg/kg per oral, diphenhydramine 1 mg/kg IV, hydrocortisone 1 mg/kg IV, ondansetron 0,15 mg/kg IV/per oral) dapat menurunkan switching rate peg-asparaginase ke produk lain (menurun dari 21% menjadi 7% setelah penambahan premedikasi).

Kesimpulan studi publikasi :

1. Advani, 2021 menunjukkan adanya penurunan kejadian reaksi hipersensitivitas grade 3-4 pada protokol studi CALGB dibandingkan dengan protocol studi CALGB 10403 setelah amandemen yaitu dengan penambahan premedikasi kortikosteroid, asetaminofen, dan difenhidramin (10% vs 4%)
2. Cooper, 2019 dosis yang direkomendasikan untuk premedikasi adalah Diphenhydramine (1 mg/kg, max 50 mg/dose) dan famotidine (1 mg/kg/dose, max 20 mg) atau ranitidine (2 mg/kg/dose, max 150 mg). Hasil studi menunjukkan adanya penurunan reaksi hipersensitivitas klinis pada pasien dengan premedikasi dibandingkan dengan pasien tanpa premedikasi (7,4% vs 17,2%) serta penurunan tingkat efek samping akut pada pasien dengan premedikasi dibandingkan dengan pasien tanpa premedikasi (5,9% vs 17,2%)
3. Lasasso, 2019 menunjukkan bahwa kejadian reaksi alergi grade 3-4 pada pasien yang menerima premedikasi (methylprednisolone, acetaminophen and diphenhydramine) lebih rendah dibandingkan pasien tanpa premedikasi (3,7% vs 5,2%)
4. Menunjukkan adanya penurunan switching rate antara sebelum implementasi premedikasi vs setelah implementasi premedikasi (21% vs 7%). Premedikasi yang diberikan yaitu Acetaminophen 15 mg/kg PO, Diphenhydramine 1 mg/kg IV, Hydrocortisone 1 mg/kg IV dan Ondansetron 0,15 mg/kg IV/PO,

EVALUASI
Penilaian Manfaat – Risiko

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi jurnal terpublikasi, Oncaspar memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut:

a. Aspek yang menguntungkan
   i. Pemberian premedikasi kortikosteroid, asetaminofen dan difenhidramin dapat menurunkan kejadian reaksi hipersensitivitas grade 3-4, yaitu menurun dari 10% menjadi 4% setelah penambahan premedikasi.
   ii. Pemberian premedikasi premedikasi diphenhydramine (1 mg/kg, maksimum 50 mg/dosis, IV atau oral) dan famotidine (1 mg/kg/dosis, maksimum 20 mg, IV atau oral) atau ranitidine (2 mg/kg/dosis, maksimum 150 mg, oral), menurunkan reaksi hipersensitivitas klinis yang memerlukan substitusi obat dibandingkan pasien tanpa premedikasi (7,4% vs 17,2%; RR 0,427; 95% CI 0.27–0.69; P = 0,028) dan menurunkan acute adverse events (5,9% vs 17,2%; RR=0,342; 95% CI 0.2–0.58; P = 0,017).
   iii. Pemberian premedikasi (acetaminophen 10–15 mg/kg orally, diphenhydramine 1 mg/kg orally or intravenously, dan methylprednisolone 1 mg/kg intravenously) 1 jam sebelum pemberian peg asparaginase, kejadian reaksi alergi grade 3-4 lebih rendah dibandingkan tanpa premedikasi (3,7% vs 5,2%)
   iv. Pemberian premedikasi (acetaminophen 15 mg/kg per oral, diphenhydramine 1 mg/kg IV, hydrocortisone 1 mg/kg IV) dapat menurunkan switching rate peg-asparaginase ke produk lain (menurun dari 21% menjadi 7% setelah penambahan premedikasi).

b. Aspek yang tidak menguntungkan : NA

c. Ketidakpastian dan keterbatasan : NA

Kesimpulan evaluasi manfaat – risiko:

Secara keseluruhan penggunaan Oncaspar menunjukkan manfaat yang signifikan dalam pengobatan leukimia, khususnya dalam konteks penurunan reaksi hipersensitivitas berat dan efek samping akut ketika diberikan premedikasi yang sesuai. Pemberian premedikasi secara sistematis dapat meningkatkan tolerabilitas terapi dan menurunkan risiko reaksi merugikan sehingga mempertahankan keberlanjutan penggunaan peg-asparaginase dalam protokol terapi kanker.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi Oncaspar diterima dengan **posology yang diajukan** sebagai berikut:

Posologi :

Oncaspar should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored for any adverse reactions throughout the administration period (see section 4.4).

Posology

Oncaspar is usually administered as part of combination chemotherapy protocols with other antineoplastic agents (see also section "Interaction with other medicinal products and other forms of interaction").

Recommended premedication

Premedicate patients with paracetamol, an H-1 receptor blocker (e.g. diphenhydramine), and an H-2 receptor blocker (e.g. famotidine) 30-60 minutes prior to administration of Oncaspar to decrease the risk and severity of both infusion and hypersensitivity reactions (see section 4.4).

Paediatric patients and adults ≤21 years

The recommended dose in patients with a body surface area (BSA) ≥ 0.6 m2 and who are ≤21 years of age is 2,500 U of pegaspargase (equivalent to 3.3 ml Oncaspar)/m2 body surface area every 14 days.

Children with a body surface area 21 yearsUnless otherwise prescribed, the recommended posology in adults aged >21 years is 2,000 U of pegaspargase (equivalent to 2.67 ml Oncaspar)/m^2 body surface area every 14 days.Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of pegaspargase. If asparaginase activity values fail to reach target levels, a switch to a differentasparaginase preparation could be considered (see section "Special warnings and precautions for use").

Special populations

Renal impairment

As pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no dose adjustment is necessary in patients with renal impairment.

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

Elderly

There are limited data available for patients older than 65 years.

Method of administration

Oncaspar can be given by intramuscular (IM) injection or intravenous (IV) infusion.For smaller volumes, the preferred route of administration is intramuscular. When Oncaspar is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If higher volume is given, the dose should be divided and given at several injection sites. Intravenous infusion of Oncaspar is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution. The diluted solution can be given together with an already-running infusion of either sodium chloride 9 mg/ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of Oncaspar. For instructions on reconstitution and dilution of this medicinal product before administration, see section "Special precautions for disposal and other handling"