Public Assessment Report
XPOVIO

INFORMASI PRODUK

Nama obat	:	**XPOVIO**
Bentuk sediaan	:	TABLET SALUT SELAPUT
Zat aktif	:	Tiap tablet salut selaput mengandung: Selinexor 20 mg
Kemasan	:	Dus, 4 blister @ 6 tablet Dus, 4 blister @ 8 tablet Dus, 4 blister @ 5 tablet Dus, 4 blister @ 4 tablet
Pendaftar	:	PT. Mecosin Indonesia, Bogor, Indonesia
Produsen	:	Diproduksi oleh Catalent CTS LLC, Missouri, USA dikemas primer oleh Carton Services Incorporated T/A Pharma Packaging Solutions, Clinton, USA, dikemas sekunder oleh Carton Services Incorporated T/A Pharma Packaging Solutions Clinton USA, dan Bollore Logistics Singapore PTE. Ltd., Singapore direlease oleh Mias Pharma Limited Dublin, Ireland
Kategori Registrasi	:	Registrasi obat dengan zat aktif baru
Indikasi yang diajukan:	:	*XPOVIO is a prescription medicine used:* ● *In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.* ● *In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.* ● *For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.*
Posologi yang diajukan	:	*In Multiple Myeloma (MM):* ● *In combination with bortezomib and dexamethasone (SVd), the recommended dosage of XPOVIO is 100 mg taken orally once weekly (QW) on Day 1 of each week until disease progression or unacceptable toxicity in combination with: bortezomib 1.3 mg/m2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off and dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week.* ● *In combination with dexamethasone (Sd), the recommended dosage of XPOVIO is 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity in combination with dexamethasone 20 mg taken orally with each dose of XPOVIO on Days 1 and 3 of each week.* *In diffuse large B-cell lymphoma (DLBCL):* ● *The recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.*

PENGANTAR

XPOVIO merupakan obat dengan zat aktif selinexor, berdasarkan studi nonklinis selinexor menghambat ekspor protein penekan tumor (TSP), pengatur pertumbuhan, dan protein mRNA onkogenik secara reversibel melalui pemblokiran exportin 1 (XPO1). Penghambatan XPO1 oleh

selinexor menyebabkan akumulasi TSP dalam nukleus dan penurunan beberapa onkoprotein, seperti c-myc dan cyclin D1, penghentian siklus sel, dan apoptosis sel kanker. Selinexor menunjukkan aktivitas pro-apoptotik in vitro pada sel *multiple myeloma* dan menunjukkan aktivitas antitumor pada model xenograft murine dari *multiple myeloma* dan *diffuse large B cell lymphoma*.

Multiple myeloma ditandai oleh keberadaan plasmacytoma di sumsum tulang (tumor sel plasma) dan produksi berlebih imunoglobulin monoklonal (IgG, IgA, IgD, atau IgE), atau protein Bence-Jones (rantai ringan kappa atau lambda), sementara produksi imunoglobulin normal terganggu.

Multiple myeloma (MM) merupakan penyakit langka dan tidak dapat disembuhkan yang menyerang sel plasma, dan umumnya terjadi pada orang dewasa berusia di atas 60 tahun (usia median saat diagnosis adalah sekitar 70 tahun). MM merupakan keganasan hematologi kedua yang paling sering ditemukan setelah limfoma non-Hodgkin, dengan menyumbang sekitar 1% dari seluruh kasus kanker dan 2% dari seluruh kematian akibat kanker. Pada tahun 2018, angka kejadian multiple myeloma di tingkat global adalah sekitar 1,7 per 100.000 penduduk per tahun (Ferlay, 2019). Data Global Cancer Observatory (GLOBOCAN) bahwa angka kejadian multiple myeloma di Indonesia relatif rendah, dengan estimasi insidensi sekitar 1,2 per 100.000 penduduk per tahun.

Mengingat registrasi XPOVIO merupakan registrasi zat aktif baru, saat ini evaluasi difokuskan pada evaluasi data uji non klinik, klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

Xpovio mengandung zat aktif selinexor 20 mg. Obat mengandung eksipien microcrystaline cellulose, croscarmellose sodium, povidone K30, colloidal silico dioxide, sodium lauryl sulfate, magnesium stearate, bahan penyalut, air.

Zat Aktif

Zat aktif merupakan Serbuk atau padatan putih hingga putih kekuningan, selinexor telah dilakukan karakterisasi sifat umumnya, diantaranya pemerian, *polimorfisme, kelarutan, titik leleh, pKa,dan steorisme. S*elinexor sukar larut dalam air dan mudah larut dalam dimethyl sulfoxide (DMSO), dengan titik leleh ~178^{o}C, memiliki nilai pKa 10.20 ± 0.07 (dalam air, dengan gelombang *spectrophotometric* pada 256 nm). Selinexor memiliki pusat non kiral dengan Cis atu Z olefin isomer.

Selinexor yang digunakan diperoleh dengan menggunakan KPT-482, KPT-472, dan KPT-459 sebagai bahan awal dan diproses melakui 4 tahap proses reaksi. Telah dilakukan kontrol terhadap tahapan kritis dan intermediate kritikal selama proses sintesa.

Struktur kimia *selinexor* telah ditunjukkan berdasarkan uji *elemental analysis, mass spectrometry (MS), proton (1H), carbon (13C), dan Fluorine (F19) nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), Spektro UV, X-ray Powder Diffraction (XRPD) Analysis, dan Single Crystal X-ray Diffraction (SCXRD).*

Spesifikasi zat aktif telah ditetapkan terdiri dari pemerian (visual), identifikasi, kadar (HPLC), senyawa sejenis (HPLC), sisa pelarut (GC), sisa bahan yang digunakan dalam sintesis, *elemental impurities*, kadar air, dan sisa pijar, distribusi ukuran partikel, dan mikrobial.
Uji stabilitas zat aktif telah dilakukan dan menunjukkan zat aktif stabil ketika disimpan pada suhu di bawah 25^{o}C selama 60 bulan.

Obat jadi

Obat jadi diproduksi dalam bentuk tablet salut selaput yang dibuat secara granulasi kering. Proses pembuatannya obat dilakukan mulai dari penampuran, pencetakan tablet, pembuatan larutan penyalut, penyalutan, dan pengemasan. Telah dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process controls* yang dilakukan pada masing-masing tahapan tersebut. Validasi proses telah dilakukan terhadap 3 bets skala komersil untuk masing-masing kekuatan. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu pemerian (visual), identifikasi (HPLC), kadar (HPLC), keseragaman kandungan (HPLC), pengotor (HPLC), disolusi, kadar air, dan batas mikroba. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets kala komersil dengan hasil memenuhi spesifikasi dan tidak ada perubahan signifikan. Penyimpanan produk yang dapat disetujui adalah Store below 30 ℃ selama 60 bulan.

Kesimpulan
Dari aspek mutu, XPOVIO tablet salut selaput dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik
Hasil evaluasi terhadap studi non klinik yang diserahkan sebagai berikut:

- Studi non-klinik menunjukkan selinexor mampu meningkatkan apoptosis sel kanker melalui penghambatan exportin-1 (XPO1) secara in vitro. Uji toksisitas secara in vivo menyebabkan efek samping seperti penurunan berat badan, hipoplasia hematologis / limfoid, dan gangguan gastrointestinal. Selinexor tidak bersifat mutagenik atau klastogenik.
- Selinexor menghambat arus hERG (IC50≈20.6 μM), menunjukkan selektivitas sekitar 1000 kali lipat dibandingkan potensi selinexor untuk menghambat ekspor nuklear yang bergantung pada XPO1 dan nilai IC50 diperkirakan sekitar 274 kali lebih tinggi daripada free unbound Cmax manusia setelah dosis 80 mg (0,033 μg/mL; berdasarkan pengikatan protein plasma manusia sebesar 95,1% dan rata-rata Cmax sebesar 0,68 μg/mL).
- Administrasi oral selinexor pada tikus hamil menyebabkan toksisitas pada induk (penurunan rata-rata kenaikan berat badan dan penurunan rata-rata konsumsi makanan) dan efek pada perkembangan embrio (penurunan berat rata-rata janin jantan, betina, dan gabungan, yang berkorelasi dengan penurunan berat rata-rata rahim, dan variasi perkembangan tulang NOAEL untuk toksisitas induk dan toksisitas perkembangan embrio adalah 0,25 mg/kg/hari (KNC-G 13-008), yang setara dengan ~0,02× paparan manusia (AUC) yang terkait dengan dosis 80 mg.
- Dosis maksimum yang ditoleransi/ maximum tolerated dose (MTD) adalah 100 mg/kg (600 mg/m^2) pada tikus Sprague Dawleyuntuk kedua jenis kelamin (rata-rata keseluruhan (jantan dan betina) AUClast = 65,9 μg•h/mL; Cmax = 15,9 μg/mL).
- Setelah pemberian suspensi oral, laju penyerapan terjadi cepat pada tikus, dengan nilai waktu hingga konsentrasi maksimum (tmax) biasanya kurang dari 1 jam, dan sedikit lebih lama pada monyet, dengan nilai tmax rata-rata antara 1 dan 3 jam.
- Tidak ada efek pada pengamatan SSP atau pernapasan yang dicatat pada ≤50 mg/kg
- Efek pada suhu tubuh kemungkinan terkait dengan penurunan sitokin pirogenik seperti IL1, IL6, atau TNFα yang merupakan efek yang dikenal dari penghambatan XPO1. Dalam kondisi penelitian ini, NOEL untuk selinexor adalah 10 mg/kg.
- Efek pada pernapasan menunjukkan penurunan yang signifikan tergantung dosis (*dose-dependent manner*) ($p<0.05$) dalam volume per menit (total volume yang dihirup dalam 1 menit), frekuensi pernapasan, dan volume tidal diamati pada ≥10 mg/kg hingga 300 menit paska pemberian dosis. Penurunan maksimal dalam volume per menit adalah 29,7% dan 33,4% dibandingkan dengan volume per menit baseline pada 10 dan 50 mg/kg, masing masing (NOEL=2 mg/kg).
- Studi pada hewan coba tikus menunjukkan bahwa secara keseluruhan, dalam studi toksisitas selama 2 dan 4 minggu, No Observed Adverse Effect Level (NOAEL) adalah 2 mg/kg.
- Studi pada hewan coba monyet menunjukkan bahwa secara keseluruhan, efek terkait dengan pengobatan yang diamati dalam studi toksisitas selama 13 minggu meliputi penurunan berat badan, efek gastrointestinal, dan deplesi limfoid/hematologis yang sebagian atau sepenuhnya pulih setelah penghentian pengobatan (penurunan konsumsi makanan dan sitopenia secara kualitatif serupa dengan yang diamati pada pasien).
- Selinexor tidak bersifat mutagenik atau klastogenik

Studi Klinik

Data yang diserahkan terdiri dari:

1. Studi klinik fase 1 KCP-330-001 pada pasien dengan hematological malignancies
2. Satu studi klinik fase 2 (STOMP KCP-330-017 (n=43)) dan satu studi klinik fase 3 (BOSTON KCP 330-023 (n=402)) untuk mendukung indikasi *"In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."*

3. Satu studi klinik fase 2 (KCP-330-012 STORM (n=123)) untuk mendukung indikais "*In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti- CD38 monoclonal antibody*."
4. Studi *ongoing* klinik fase 2 SADAL KCP-330-009 (n=127) untuk mendukung indikasi *"For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant."*

Hasil evaluasi terhadap studi yang diserahkan sebagai berikut.
Efikasi :

1. Studi klinik fase 1 KCP-330-001 pada pasien dengan hematological malignancies menunjukkan bahwa pemberian selinexor pada dosis 3-80 mg/m2 atau 5-150 mg diperoleh nilai Tmax pada siklus pertama 1,9-4,0 jam dan t1/2 6 jam. Kadar plasma (Cmax dan AUC) meningkat proporsional bersama peningkatan dosis. Tidak terjadi akumulasi obat pada pemberian berulang selinexor secara oral. Efek selinexor terhadap penghambatan XPO-1 ditunjukkan dengan adanya peningkatan mRNA XPO-1. Induksi mRNA XPO-1 mulai meningkat 2 jam setelah pemberian selinexor dan mencapai puncak dalam waktu 4-8 jam maksimal pada dosis lebih besar sama dengan 12 mg/m2 (~20 mg).
2. Indikasi "*In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy*."
   a. Hasil studi klinik fase 2 STOMP KCP-330-017 (n=43) yang membandingkan pemberian selinexor 80 mg dan 100 mg sekali seminggu serta selinexor 60 mg dan 80 mg dua kali seminggu dengan kombinasi bortezomib 1,3 mg/m2 dan dexamethason 40 mg pada pasien dewasa dengan *multiple myeloma* yang telah menerima setidaknya salah satu dari terapi Bortezomib, Carfilzomib, Ixazomib, Daratumumab, Lenalidomide, dan Pomalidomide sebelumnya. Zat aktif Carfilzomib belum disetujui di Indonesia. Hasil studi menunjukkan:
      - Respon dilaporkan pada 40 pasien *Multiple Myeloma* dengan nilai ORR 63% (95% CI: 47% to 76%), mencakup 3 (8%) complete responses (CRs), 9 (23%) very good partial responses (VGPRs), dan 13 (33%) partial responses (PRs). Sejumlah 7 (18%) pasien memiliki minimal response (MR). Nilai Clinical Benefit Rate adalah 80% (95% CI: 65% to 90%). Progresi penyakit pada saat on therapy dilaporkan pada 1 pasien.
      - Nilai median durasi respon pertama adalah 1,2 bulan (IQR:1,2-1,7 bulan).
      - Nilai median PFS (Progression-free survival) pada kelompok pasien dengan multiple myeloma yang refrakter terhadap proteasome inhibitors (PI) adalah 7 bulan. Nilai median OS belum tercapai.
   b. Hasil studi klinik fase 3 BOSTON KCP 330-023 (n=402) yang membandingkan pemberian Selinexor 100 mg dikombinasi bortezomib 1,3 mg/m2 dan dexamethasone 20 mg dengan kelompok yang diberikan bortezomib 1,3 mg/m2 dan dexamethasone 20 mg pada pasien dengan relaps atau refraktori multiple myeloma (RRMM) selama 5 tahun menunjukkan:
      - Terapi kombinasi selinexor dengan bortezomib dan dexamethasone (SVd) meningkatkan median PFS yang signifikan dibanding regimen standar bortezomib dan dexamethasone (Vd) (13,93 bulan vs 9,46 bulan, HR=0,70; p=0,0075) pada pasien *multiple myeloma* dewasa yang telah mendapatkan setidaknya satu terapi sebelumnya.
      - Nilai *overall response rate (ORR)* pada kelompok selinexor+bortezomib+dexamethasone (SVd) lebih tinggi dibandingkan dengan regimen standar bortezomib+dexamethasone (Vd) (76,4% vs 62,3%, p=0,0012).
3. Indikasi "*In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti- CD38 monoclonal antibody*."
   a. Hasil studi klinik fase 2 KCP-330-012 STORM (n=123) menunjukkan bahwa pemberian selinexor 80 mg ditambah dexamethasone 20 mg secara peroral pada pasien *multiple myeloma* yang refrakter terhadap tiga kelas obat (*proteasome inhibitor / PI, immunomodulatory drug, dan Daratumumab*) dan telah terpapar lima jenis obat (lenalidomide, pomalidomide, bortezomib, carfilzomib, dan daratumumab) sebelumnya memberikan efikasi berdasarkan parameter:
      - ORR (*Overall Response Rate*) per IRC (mITT Analysis Population) sebesar 26,2% (95% CI: 18,7, 35,0), dengan persentase subjek yang mengalami complete response dan very good partial response masing-masing sebesar 1,6% dan 4,9%.
      - *Median duration of response (DOR)* per IRC pada pasien yang mencapai minimal respons

atau lebih baik yaitu 4,4 bulan (95% CI: 3,7, 10,8). Namun tidak adanya kontrol dalam studi ini menyebabkan keterbatasan dalam menentukan apakah kemanfaatan dan efek samping disebabkan oleh selinexor, perkembangan alamiah/kondisi penyakit, atau terapi sebelumnya.

- Mayoritas pasien (97,5%) dalam studi tersebut sebelumnya mendapatkan terapi dan refrakter terhadap terapi carfilzomib, namun carfilzomib belum terdaftar dan beredar di Indonesia.

4. Indikasi *"For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant."*
   a. Studi *ongoing* klinik fase 2 SADAL KCP-330-009 (n=127) mengevaluasi efikasi selinexor 60 mg dua kali seminggu (BIW pada hari ke-1 dan ke-3) pada pasien dengan Diffuse Large B-Cell Lymphoma (DLBCL) yang relaps atau refrakter.
      - Berdasarkan data interim hingga 54 minggu, hasil studi menunjukkan *Overall Response Rate* (ORR) sebesar 28,3% dimana 11,8% menunjukkan *complete response*, 16,5% *partial response*, dan 8,7% *stable disease* dan *Median Duration of Response (DOR)* adalah 9,3 bulan (95% CI: 4,8; 23.0)

Keamanan:
Hasil evaluasi keamanan yang dilaporkan pada studi STOMP KCP-330-017, BOSTON KCP 330-023, studi klinik fase 2 KCP-330-012 STORM, SADAL KCP-330-009 menunjukkan *Adverse events* yang paling seringteramati neurophaty, kelelahan, mual, trombositopenia, lymphopenia, anemia, neutropenia, penurunan nafsu makan, anemia.

- KCP 330-023 BOSTON :
  - Trombositopenia, kelelahan, mual, anemia, penurunan nafsu makan, penurunan berat badan, katarak, asthenia, dan muntah teramati lebih sering terjadi (≥10% lebih tinggi) pada kelompok SVd dibandingkan kelompok Vd
  - Pasien yang mendapat SVd memiliki risiko lebih rendah mengalami efek samping neuropati perifer yang berat atau Grade ≥2 dibandingkan pasien yang mendapat pengobatan Vd (p value=0,0013). Hanya 21% pasien di kelompok SVd yang mengalami efek samping ini, sementara di kelompok Vd, 34,3% pasien mengalaminya
- KCP-330-012 / STORM Part II A:
  - AE yang paling umum dilaporkan adalah trombositopenia (74%), anemia (46%), mual (44%), kelelahan (42%), dan penurunan nafsu makan (34%). SAE yang paling umum dilaporkan adalah pneumonia (8%), sepsis (7%), dan trombositopenia (6%).
  - AE yang menyebabkan penghentian pengobatan: 27% pasien menghentikan pengobatan karena AE yang terkait dengan selinexor. AE yang paling umum menyebabkan penghentian pengobatan adalah trombositopenia (8%), kelelahan (4%), dan anemia (3%).
  - Kematian sebanyak 21% pasien selama penelitian, dengan sebagian besar kematian disebabkan oleh progresi penyakit.
- KCP-330-009 SADAL
  - Adverse events yang paling umum (≥20%) efek samping yang muncul akibat pengobatan (TEAEs) adalah trombositopenia (61,4%), mual (58,3%), kelelahan (47,2%), anemia (42,5%), penurunan nafsu makan (37,0%), diare (35,4%), sembelit (30,7%), neutropenia (29,9%), berat badan menurun (29,9%), muntah (29,1%), pireksia (22,0%), dan astenia (21,3%).
  - Dalam populasi mITT, 125 (98,4%) pasien melaporkan setidaknya 1 TEAE. Empat puluh tiga (33,9%) pasien mengalami TEAE yang mengakibatkan penurunan dosis, 77 (60,6%) pasien mengalami TEAE yang mengakibatkan penghentian obat, 22 (17,3%) pasien mengalami TEAE yang mengakibatkan penghentian pengobatan dalam penelitian, dan 5 (3,9%) pasien mengalami TEAE yang berakibat fatal. Dari 22 pasien yang menghentikan selinexor karena TEAE, 5 (18,5%) menunjukkan tanda-tanda progresi penyakit pada saat penghentian pengobatan.

EVALUASI
Penilaian Manfaat-Risiko

XPOVIO merupakan obat dengan zat aktif selinexor yangmenunjukkan aktivitas pro-apoptotik in vitro pada sel *multiple myeloma* dan menunjukkan aktivitas antitumor pada model xenograft murine dari *multiple myeloma* dan *diffuse large B cell lymphoma*. Multiple myeloma (MM) merupakan penyakit

langka dan tidak dapat disembuhkan yang menyerang sel plasma, dan umumnya terjadi pada orang dewasa berusia di atas 60 tahun (usia median saat diagnosis adalah sekitar 70 tahun). Angka kejadian multiple myeloma di tingkat global adalah sekitar 1,7 per 100.000 penduduk per tahun

Berdasarkan data mutu yang telah dievaluasi sebelumnya, produksi zat aktif dan produk jadi Xpovio tablet salut selaput telah dikontrol dengan baik mulai dari bahan baku, proses pembuatan, hingga tahap akhir sehingga dapat menghasilkan XPOVIO yang memenuhi spesifikasi pelulusan dan *shelf-life*. Data stabilitas yang tersedia mendukung stabilitas XPOVIO pada penyimpanan 30 ℃ selama 60 bulan.

Berdasarkan data khasiat dan keamanan yang diperoleh dari hasil studi klinik, vaksin Xpovio memiliki efek yang menguntungkan, efek yang tidak menguntungkan, ketidakpastian dan keterbatasan sebagai berikut:

a. Aspek yang menguntungkan:
   - Studi klinik BOSTON KCP 330-023 (n=402) pada pasien relaps atau refraktori multiple myeloma (RRMM) , efikasi pemberian selinexor+bortezomib+dexamethasone lebih baik dibandingkan pemberian bortezomib+dexamethasone dengan median PFS 13,93 bulan vs 9,46 bulan, nilai ORR 76,4% vs 62,3%
   - Studi klinik SADAL KCP-330-009 (n=127) pada pasien Diffuse Large B-Cell Lymphoma (DLBCL) yang relaps atau refrakter, nilai ORR untuk pemberian selinexor 28,3%, dimana CR dicapai pada 11,8% pasien dan stable disease pada 8.7%.
   - Profil keamanan secara umum dapat ditoleransi dengan baik, • Pasien yang mendapat Selinexor memiliki risiko lebih rendah mengalami efek samping neuropati perifer yang berat atau Grade ≥2 dibandingkan pasien yang yang tidak mendapatkan selinexor
   - Adverse events yang teramati neurophaty, fatigue, nausea, thrombocytopenia, lymphopenia, anemia, neutropenia.

b. Aspek yang tidak menguntungkan:
   - Adverse events yang paling sering teramati neuropathy, kelelahan, mual, trombositopenia, lymphopenia, anemia, neutropenia, penurunan nafsu makan, anemia..

c. Ketidakpastian dan keterbatasan:
   - studi SADAL KCP-330-009 merupakan studi Fase II *on-going* yang perlu dilanjutkan untuk memberikan kepastian efikasi dan keamanan yang lebih kuat untuk mendukung indikasi *For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.*"

Kesimpulan Manfaat-Risiko

Secara keseluruhan obat ini menunjukkan kemanfaatan penggunaan kombinasi dengan *bortezomib dan dexamethasone (SVd) atau kombinasi dengan dexamethasone (Sd) pada p*engobatan penyakit *Multiple Myeloma (MM)* dan penggunaan tunggal untuk pengobatan *diffuse large B-cell lymphoma (DLBCL)*.

Risiko efek samping termasuk efek samping serius perlu dikomunikasikan dan dicantumkan dalam Informasi Produk; Pendaftar wajib menyerahkan laporan lengkap studi SADAL KCP-330-009 untuk pemastian lebih lanjut efikasi dan keamanan selinexor dan melakukan pemantauan farmakovigilans dan pelaporan efek samping obat ke Badan POM.

Berdasarkan hal tersebut di atas, Xpovio tablet salut selaput dipertimbangkan memiliki manfaat yang lebih besar dibanding risikonya.

KEPUTUSAN

Berdasarkan hal tersebut di atas, registrasi zat aktif baru XPOVIO Tablet Salut Selaput diterima dengan indikasi sebagai berikut :

XPOVIO is a prescription medicine used:

In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti CD38 monoclonal antibody.

For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.

Dengan ketentuan:

1. Diperlukan laporan lengkap studi SADAL KCP-330-009 untuk pemastian lebih lanjut efikasi dan keamanan selinexor.
2. Secara berkala menyerahkan data Keamanan Paska Pemasaran (Periodic Safety Update Report/PSUR) ke Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif (Kelompok Substansi Pengawasan Keamanan Obat, Narkotika, Psikotropika, dan Prekursor).

Public Assessment Report

XPOVIO

PRODUCT INFORMATION

Product Name	:	XPOVIO
Dosage Form	:	Film-Coated Tablet
Active Ingredient	:	Each film-coated tablet contains Selinexor 20 mg
Packaging	:	Box, 4 blisters @ 6 tablets Box, 4 blisters @ 8 tablets Box, 4 blisters @ 5 tablets Box, 4 blisters @ 4 tablets
Registrant	:	PT. Mecosin Indonesia, Bogor, Indonesia
Manufacturer	:	Manufactured by Catalent CTS LLC, Missouri, USA Primary packaging by Carton Services Incorporated T/A Pharma Packaging Solutions, Clinton, USA Secondary packaging by Carton Services Incorporated T/A Pharma Packaging Solutions, Clinton, USA and Bollore Logistics Singapore PTE. Ltd., Singapore Released by Mias Pharma Limited, Dublin, Ireland
Registration Category	:	New Active Substance Registration
Proposed Indications	:	XPOVIO is a prescription medicine used: • In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. • For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.

Proposed Dosage and Administration : In Multiple Myeloma (MM):

- In combination with bortezomib and dexamethasone (SVd), the recommended dosage of XPOVIO is 100 mg taken orally once weekly (QW) on Day 1 of each week until disease progression or unacceptable toxicity in combination with: bortezomib 1.3 mg/m2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off and dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week.
- In combination with dexamethasone (Sd), the recommended dosage of XPOVIO is 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity in combination with dexamethasone 20 mg taken orally with each dose of XPOVIO on Days 1 and 3 of each week.

In Diffuse Large B-cell Lymphoma (DLBCL):

- The recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.

INTRODUCTION

XPOVIO contains the active substance selinexor. Based on non-clinical studies, selinexor reversibly inhibits the export of tumor suppressor proteins (TSP), growth regulators, and oncogenic mRNA-binding proteins through the blockade of exportin 1 (XPO1). Inhibition of XPO1 by selinexor causes the accumulation of TSP in the nucleus and reduction of several oncoproteins, such as c-myc and cyclin D1, leading to cell cycle arrest and apoptosis of cancer cells. Selinexor exhibits pro-apoptotic activity in vitro on multiple myeloma cells and demonstrates antitumor activity in murine xenograft models of multiple myeloma and diffuse large B-cell lymphoma (DLBCL).

Multiple myeloma is characterized by the presence of bone marrow plasmacytomas (plasma cell tumors) and overproduction of monoclonal immunoglobulins (IgG, IgA, IgD, or IgE), or Bence-Jones proteins (kappa or lambda light chains), while normal immunoglobulin production is impaired. MM is a rare and incurable disease that affects plasma cells, commonly seen in adults over 60 years of age (median age at diagnosis is approximately 70 years). MM is the second most common hematologic malignancy after non-Hodgkin lymphoma, accounting for about 1% of all cancers and 2% of all cancer-related deaths. In 2018, the global incidence rate of multiple myeloma was approximately 1.7 per 100,000 population per year (Ferlay, 2019). According to the Global Cancer Observatory (GLOBOCAN), the incidence rate in Indonesia is relatively low, estimated at around 1.2 per 100,000 population per year.

Since XPOVIO is a new active substance registration, current evaluation focuses on the assessment of non-clinical, clinical, and quality data to further demonstrate the efficacy, safety, and quality of the product.

QUALITY ATTRIBUTES

XPOVIO contains selinexor 20 mg as the active substance. The product also includes the following excipients such as microcrystalline cellulose, croscarmellose sodium, povidone K30, colloidal silicon dioxide, sodium lauryl sulfate, magnesium stearate, coating material, and water.

Active Substance

The active substance is a white to off-white powder. Selinexor has undergone characterization of its general properties, including description, polymorphism, solubility, melting point, pKa, and stereochemistry. Selinexor is poorly soluble in water but readily soluble in dimethyl sulfoxide (DMSO), with a melting point of approximately 178°C. It exhibits a pKa value of 10.20 ± 0.07 (in water, with a spectrophotometric absorption at 256 nm). Selinexor contains a non-chiral center and exists as a Cis or Z olefin isomer.

The Selinexor used is obtained using KPT-482, KPT-472, and KPT-459 as starting materials and processed through four stages of reaction. Critical stages and critical intermediates have been controlled during the synthesis process.

The chemical structure of selinexor has been determined through elemental analysis, mass spectrometry (MS), proton (1H), carbon (13C), and fluorine (F19) nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), UV spectroscopy, X-ray powder diffraction (XRPD) analysis, and single Crystal X-ray Diffraction (SCXRD).

The specifications for the active substance have been established, including description (visual), identification, potency (HPLC), related substances (HPLC), residual solvents (GC), residual reagents used in synthesis, elemental impurities, water content, ash residue, particle size distribution, and microbial limits.

Stability testing of the active substance has been conducted, demonstrating that the active substance remains stable when stored at temperatures below 25°C for 60 months.

Finished Product

The finished product is manufactured in the form of film-coated tablets produced through a dry granulation process. The production process involves mixing, tablet compression, coating solution preparation, coating, and packaging. Identification of critical stages has been performed, including in-process controls conducted at each stage. Process validation has been carried out for three commercial-scale batches of each strength. The validation results indicate that the process is capable of producing a finished product that meets the established acceptance criteria.

The specifications for the finished product have been established, including description (visual), identification (HPLC), potency (HPLC), content uniformity (HPLC), impurities (HPLC), dissolution, water content, and microbial limits. The parameters in the specification are selected based on the physicochemical characteristics and critical properties of the active substance, taking into account, among other factors, the results of clinical trial batches, and long-term stability data. The analytical methods used have been validated. The batch analysis results meet the required specifications.

Stability data from three commercial-scale batches show results that meet the specifications with no significant changes. The product is approved for storage below 30°C for up to 60 months.

Conclusion

From a quality perspective, XPOVIO film-coated tablets can be considered acceptable for approval.

EFFICACY AND SAFETY ASPECTS

Non-Clinical Studies

The evaluation results of the submitted non-clinical studies are as follows:

- The non-clinical studies demonstrate that selinexor induces apoptosis in cancer cells through the inhibition of exportin-1 (XPO1) in vitro. Toxicity studies conducted in vivo revealed side effects such as weight loss, hematologic/lymphoid hypoplasia, and gastrointestinal disturbances. Selinexor is not mutagenic or clastogenic.
- Selinexor inhibits the hERG current (IC50 ≈ 20.6 μM), showing a selectivity approximately 1000 times higher compared to its potential to inhibit XPO1-dependent nuclear export, with the IC50 estimated to be about 274 times higher than the free unbound human Cmax after an 80 mg dose (0.033 μg/mL; based on 95.1% human plasma protein binding and an average Cmax of 0.68 μg/mL).
- Oral administration of selinexor in pregnant rats resulted in maternal toxicity (reduced average weight gain and decreased average food consumption) and effects on embryo development (reduced average fetal weight for both male and female fetuses, as well as the combined group, correlating with a decrease in average uterine weight, and bone development variations). The NOAEL for maternal toxicity and embryo developmental toxicity was 0.25 mg/kg/day (KNC-G 13-008), which is approximately 0.02× human exposure (AUC) related to the 80 mg dose.

- The maximum tolerated dose (MTD) was found to be 100 mg/kg (600 mg/m²) in Sprague Dawley rats of both sexes (overall average AUClast = 65.9 µg·h/mL; Cmax = 15.9 µg/mL).
- Following oral suspension administration, absorption occurred rapidly in rats, with the time to maximum concentration (tmax) typically being less than 1 hour, and slightly longer in monkeys, with an average tmax between 1 and 3 hours.
- No effects on the central nervous system (CNS) or respiration were observed at doses ≤50 mg/kg.
- Effects on body temperature were likely associated with a reduction in pyrogenic cytokines such as IL-1, IL-6, or TNFα, which are known effects of XPO1 inhibition. In this study condition, the NOEL for selinexor was 10 mg/kg.
- Respiratory effects showed a dose-dependent decrease ($p<0.05$) in minute volume (total volume inhaled in 1 minute), respiratory frequency, and tidal volume observed at doses ≥10 mg/kg up to 300 minutes post-dose. The maximum decrease in minute volume was 29.7% and 33.4% compared to baseline minute volume at 10 and 50 mg/kg, respectively (NOEL = 2 mg/kg).
- Studies in rats showed that, overall, in the 2- and 4-week toxicity studies, the No Observed Adverse Effect Level (NOAEL) was 2 mg/kg.
- Studies in monkeys showed that, overall, treatment-related effects observed in the 13-week toxicity study included weight loss, gastrointestinal effects, and lymphoid/hematologic depletion, which were partially or fully recovered after treatment cessation (reduced food consumption and cytopenia qualitatively similar to that observed in patients).
- Selinexor is not mutagenic or clastogenic.

Clinical Studies

The submitted data includes the following:

1. Phase 1 Clinical Study KCP-330-001 in patients with hematological malignancies.
2. One Phase 2 Clinical Study (STOMP KCP-330-017 (n=43)) and one Phase 3 Clinical Study (BOSTON KCP-330-023 (n=402)) to support the indication: "In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."
3. One Phase 2 Clinical Study (KCP-330-012 STORM (n=123)) to support the indication: "In combination with dexamethasone, is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody."
4. Ongoing Phase 2 Clinical Study SADAL KCP-330-009 (n=127) to support the indication: "For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy, who are not eligible for hematopoietic cell transplant."

Evaluation Results of the Submitted Studies

Efficacy:

1. Phase 1 Clinical Study KCP-330-001 in patients with hematological malignancies demonstrated that selinexor administration at doses of 3-80 mg/m² or 5-150 mg resulted in a Tmax of 1.9–4.0 hours and a half-life ($t_1/_2$) of 6 hours during the first cycle. Plasma concentrations (Cmax and AUC) increased proportionally with dose escalation. No drug accumulation was observed with repeated oral dosing of selinexor. The effect of selinexor on inhibiting XPO-1 was indicated by an increase in XPO-1 mRNA. XPO-1 mRNA induction began 2 hours after selinexor administration and peaked within 4-8 hours at higher doses (≥12 mg/m², approximately 20 mg).
2. Indication: “In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.”
   a. Phase 2 Clinical Study STOMP KCP-330-017 (n=43) comparing selinexor 80 mg and 100 mg once weekly, and selinexor 60 mg and 80 mg twice weekly, with bortezomib 1.3 mg/m² and dexamethasone 40 mg in adult patients with multiple myeloma who have received at least one prior therapy with bortezomib, carfilzomib, ixazomib, daratumumab, lenalidomide, or pomalidomide (Carfilzomib is not approved in Indonesia). The study results showed:
      - Response was reported in 40 multiple myeloma patients, with an overall response rate (ORR) of 63% (95% CI: 47% to 76%), including 3 (8%) complete responses (CRs), 9 (23%) very good partial responses (VGPRs), and 13 (33%) partial responses (PRs). Seven (18%) patients had minimal response (MR). The clinical benefit rate was 80% (95% CI: 65% to 90%). Disease progression on therapy was reported in 1 patient.
      - The median duration of the first response was 1.2 months (IQR: 1.2-1.7 months).
      - The median progression-free survival (PFS) for patients with multiple myeloma refractory to proteasome inhibitors (PI) was 7 months. Median overall survival (OS) has not been reached.
   b. Phase 3 Clinical Study BOSTON KCP-330-023 (n=402) comparing the administration of selinexor 100 mg combined with bortezomib 1.3 mg/m² and dexamethasone 20 mg versus bortezomib 1.3 mg/m² and dexamethasone 20 mg alone in patients with relapsed or refractory multiple myeloma (RRMM) over 5 years showed:
      - The combination therapy of selinexor, bortezomib, and dexamethasone (SVd) significantly improved the median PFS compared to the standard bortezomib and dexamethasone regimen (Vd) (13.93 months vs 9.46 months, HR = 0.70; p = 0.0075) in adult multiple myeloma patients who had received at least one prior therapy.
      - The overall response rate (ORR) in the selinexor+bortezomib+dexamethasone (SVd) group was higher compared to the standard bortezomib+dexamethasone (Vd) group (76.4% vs 62.3%, p = 0.0012).
3. Indication: *"In combination with dexamethasone, is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody."*
   a. Phase 2 Clinical Study KCP-330-012 STORM (n=123) showed that administration of selinexor 80 mg plus dexamethasone 20 mg orally in patients with multiple myeloma who were refractory to three drug classes (proteasome inhibitors/PI,

immunomodulatory drugs, and Daratumumab) and had been exposed to five types of prior therapies (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab) demonstrated efficacy based on the following parameters:

- Overall Response Rate (ORR) per IRC (mITT Analysis Population) was 26.2% (95% CI: 18.7, 35.0), with the percentage of subjects achieving complete response (CR) and very good partial response (VGPR) being 1.6% and 4.9%, respectively.
- Median Duration of Response (DOR) per IRC for patients achieving minimal response or better was 4.4 months (95% CI: 3.7, 10.8). However, the lack of a control group in this study limits the ability to determine whether the benefits and side effects were attributed to selinexor, the natural progression of the disease, or prior therapies.
- The majority of patients (97.5%) in this study had previously received therapy and were refractory to carfilzomib; however, carfilzomib is not registered or available in Indonesia.

4. Indication: *"For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy who are not eligible for hematopoietic cell transplant."*
    a. Ongoing Phase 2 Clinical Study SADAL KCP-330-009 (n=127) is evaluating the efficacy of selinexor 60 mg twice weekly (BIW on days 1 and 3) in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
        - Based on interim data at 54 weeks, the study showed an Overall Response Rate (ORR) of 28.3%, with 11.8% showing complete response (CR), 16.5% showing partial response (PR), and 8.7% showing stable disease (SD). The Median Duration of Response (DOR) was 9.3 months (95% CI: 4.8, 23.0).

Safety:
The safety evaluation reported in the STOMP KCP-330-017, BOSTON KCP-330-023, phase 2 clinical study KCP-330-012 STORM, and SADAL KCP-330-009 studies show that the most frequently observed adverse events (AEs) were neuropathy, fatigue, nausea, thrombocytopenia, lymphopenia, anemia, neutropenia, decreased appetite, and weight loss.

- KCP 330-023 BOSTON:
    - Thrombocytopenia, fatigue, nausea, anemia, decreased appetite, weight loss, cataracts, asthenia, and vomiting were observed more frequently (≥10% higher) in the SVd group compared to the Vd group.
    - Patients receiving SVd had a lower risk of experiencing severe or Grade ≥2 peripheral neuropathy AEs compared to those receiving Vd treatment (p-value=0.0013). Only 21% of patients in the SVd group experienced this AE, whereas 34.3% of patients in the Vd group reported it.
- KCP-330-012 / STORM Part II A:
    - The most common AEs reported were thrombocytopenia (74%), anemia (46%), nausea (44%), fatigue (42%), and decreased appetite (34%). The most frequently reported serious adverse events (SAEs) were pneumonia (8%), sepsis (7%), and thrombocytopenia (6%).
    - AEs leading to treatment discontinuation: 27% of patients discontinued treatment due to AEs associated with selinexor. The most common AEs causing discontinuation were thrombocytopenia (8%), fatigue (4%), and anemia (3%).
    - 21% of patients died during the study, with the majority of deaths being attributed

to disease progression.

- KCP-330-009 SADAL:
  - The most common treatment-emergent adverse events (TEAEs) (≥20%) were thrombocytopenia (61.4%), nausea (58.3%), fatigue (47.2%), anemia (42.5%), decreased appetite (37.0%), diarrhea (35.4%), constipation (30.7%), neutropenia (29.9%), weight loss (29.9%), vomiting (29.1%), fever (22.0%), and asthenia (21.3%).
  - In the mITT population, 125 (98.4%) patients reported at least one TEAE. Forty-three (33.9%) patients experienced TEAEs that led to dose reduction, 77 (60.6%) patients experienced TEAEs that resulted in treatment discontinuation, 22 (17.3%) patients experienced TEAEs that led to discontinuation of the study medication, and 5 (3.9%) patients experienced TEAEs that were fatal. Of the 22 patients who discontinued selinexor due to TEAEs, 5 (18.5%) showed signs of disease progression at the time of treatment discontinuation.

EVALUATION

Benefit-Risk Assessment

XPOVIO, with the active ingredient selinexor, demonstrates pro-apoptotic activity in vitro in multiple myeloma cells and shows antitumor activity in a murine xenograft model of multiple myeloma and diffuse large B-cell lymphoma (DLBCL). Multiple myeloma (MM) is a rare, incurable disease that affects plasma cells, typically occurring in adults over the age of 60 (the median age at diagnosis is around 70 years). The global incidence rate of multiple myeloma is approximately 1.7 per 100,000 population per year.

Based on the quality data that has been evaluated previously, the production of the active substance and the final product XPOVIO film-coated tablets has been well-controlled from raw materials, the manufacturing process, to the final stages, ensuring the product meets the required release specifications and shelf-life. Available stability data support the stability of XPOVIO when stored at 30°C for up to 60 months.

Based on the efficacy and safety data obtained from clinical studies, XPOVIO shows beneficial effects, with adverse effects, uncertainties, and limitations outlined as follows:

a. Beneficial Aspects:
- The BOSTON KCP 330-023 clinical study (n=402) in patients with relapsed or refractory multiple myeloma (RRMM) shows that the combination of selinexor + bortezomib + dexamethasone is more effective than bortezomib + dexamethasone alone, with a median PFS of 13.93 months vs. 9.46 months, and an ORR of 76.4% vs. 62.3%.
- The SADAL KCP-330-009 clinical study (n=127) in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) shows an ORR of 28.3%, with complete responses (CR) in 11.8% of patients, and stable disease (SD) in 8.7%.
- The safety profile is generally well-tolerated: Patients receiving Selinexor had a lower risk of experiencing severe or Grade ≥2 peripheral neuropathy compared to those who did not receive selinexor.
- Common adverse events observed include neuropathy, fatigue, nausea, thrombocytopenia, lymphopenia, anemia, and neutropenia.

b. Unfavorable Aspects:
- The most frequently observed adverse events include neuropathy, fatigue, nausea, thrombocytopenia, lymphopenia, anemia, neutropenia, decreased appetite, and weight loss.

c. Uncertainties and Limitations:
   - The SADAL KCP-330-009 study is an ongoing Phase II clinical trial that requires continuation to provide stronger evidence of efficacy and safety to support the indication: *For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy, who are not eligible for haematopoietic cell transplant.*

Risk-Benefit Conclusion

Overall, this medication demonstrates therapeutic benefit when used in combination with bortezomib and dexamethasone (SVd), or with dexamethasone alone (Sd) for the treatment of Multiple Myeloma (MM), and as monotherapy for the treatment of Diffuse Large B-cell Lymphoma (DLBCL).

The risks of side effects, including serious adverse events, must be clearly communicated and included in the Product Information. The applicant is required to submit a complete report on the SADAL KCP-330-009 study to further confirm the efficacy and safety of selinexor, and to conduct pharmacovigilance monitoring and report adverse drug reactions to Badan POM.

Based on the above, Xpovio tablet is considered to have a greater benefit than risk.

CONCLUSION

Based on the above, the registration of the new active ingredient XPOVIO Film-Coated Tablet is approved with the following indications:

XPOVIO is a prescription medicine used:

In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

In combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti CD38 monoclonal antibody.

For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.

With the following conditions:

1. A complete report of the SADAL KCP-330-009 study is required for further confirmation of the efficacy and safety of selinexor.
2. Periodically submit the Post-Marketing Safety Data (Periodic Safety Update Report/PSUR) to Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif (Kelompok Substansi Pengawasan Keamanan Obat, Narkotika, Psikotropika, dan Prekursor).