Public Assessment Report
PACLIALL

INFORMASI PRODUK

Nama obat	:	PacliALL
Bentuk sediaan	:	Serbuk Injeksi Liofilisasi
Zat aktif	:	Tiap vial mengandung : Paclitaxel 100 mg (Paclitaxel Bound albumin)
Kemasan	:	Dus, 1 vial @ 100 mg
Pendaftar	:	PT. Soho Industri Farmasi
Produsen	:	Panacea Biotec Pharma Ltd., Malpur, Baddi, Dist. Solan, Himachal Pradesh, 173205, India
Kategori Registrasi	:	Registrasi obat baru yang sudah terdaftar dengan bentuk sediaan baru, indikasi dan posologi baru
Indikasi yang diajukan:	:	*1. Metastatic Breast Cancer* *Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.* *2. Non-Small Cell Lung Cancer* *Paclitaxel is indicated for the first-line treatment of locally advancedor metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgeryor radiation therapy.* *3. Adenocarcinoma of the Pancreas* *Paclitaxel is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.*

PENGANTAR

Kanker payudara merupakan kanker yang paling umum terjadi pada perempuan di seluruh dunia, termasuk di Indonesia. Berdasarkan data GLOBOCAN 2020, kanker payudara menempati urutan pertama dengan insiden sekitar 65.858 kasus baru per tahun di Indonesia, dan angka kematian mencapai 22.430 kasus.

Kanker Paru Bukan Sel Kecil (Non-Small Cell Lung Cancer / NSCLC) menyumbang sekitar 85% dari seluruh kasus kanker paru, menjadikannya tipe kanker paru yang paling sering ditemui. Kanker paru merupakan penyebab utama kematian akibat kanker secara global dan di Indonesia. GLOBOCAN 2020 mencatat sekitar 34.783 kasus baru kanker paru di Indonesia dengan angka kematian 30.843 kasus. NSCLC sering terdiagnosis pada stadium lanjut.

Adenokarsinoma pankreas merupakan bentuk paling umum dari kanker pankreas, mencakup lebih dari 90% kasus. Penyakit ini dikenal memiliki prognosis yang sangat buruk dan angka kematian yang tinggi, dengan tingkat kelangsungan hidup 5 tahun kurang dari 10%. Hal ini disebabkan karena sebagian besar kasus terdiagnosis pada stadium lanjut, ketika pembedahan tidak lagi memungkinkan. Secara global, menurut GLOBOCAN 2020, terdapat lebih dari 495.000 kasus baru kanker pankreas dan sekitar 466.000 kematian.

PacliALL serbuk liofilisasi merupakan obat dengan bentuk sediaan baru, indikasi dan posologi baru, evaluasi difokuskan pada evaluasi data klinik dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut. PacliALL adalah obat yang mengandung zat aktif Paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)) dengan kekuatan 100 mg. Paclitaxel yang menempel pada albumin manusia (human albumin), dalam bentuk partikel kecil yang dikenal sebagai nanopartikel. Paclitaxel termasuk dalam kelompok obat taxanes yang digunakan pada pengobatan kanker.

Dirilis oleh Badan POM tanggal 07 Februari 2025

Paclitaxel merupakan inhibitor mikrotubulus yang berperan dalam mempromosikan pembentukan mikrotubulus dari dimer tubulin serta menstabilkan mikrotubulus dengan mencegah depolimerisasi. Stabilitas ini menyebabkan terhambatnya reorganisasi dinamis normal dari jaringan mikrotubulus yang penting untuk fungsi seluler selama interfase dan mitosis. Paclitaxel menginduksi pembentukan susunan abnormal atau "bundel" mikrotubulus sepanjang siklus sel, serta pembentukan aster multipel mikrotubulus selama fase mitosis.

PacliALL mengandung nanopartikel albumin manusia-paclitaxel, di mana paclitaxel berada dalam bentuk non-kristalin (amorfa). Setelah pemberian secara intravena, nanopartikel tersebut dengan cepat terdisosiasi menjadi kompleks paclitaxel yang terikat albumin. Albumin diketahui memediasi transitosis caveola endotel terhadap komponen plasma, dan studi in vitro menunjukkan bahwa keberadaan albumin dalam PacliALL meningkatkan transportasi paclitaxel melintasi sel endotel.

Mengingat PacliALL serbuk injeksi merupakan obat dengan bentuk sediaan, kekuatan, indikasi dan posologi baru, maka evaluasi difokuskan pada evaluasi data non klinik, klinik dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

PacliALL adalah obat yang mengandung zat aktif Paclitaxel. Obat ini mengandung albumin, yang akan berikatan dengan Paclitaxel dan membantu paclitaxel larut dalam darah dan menembus dinding pembuluh darah menuju tumor. Albumin yang digunakan adalah larutan Human Albumin 25% yang mengandung bahan tambahan Sodium, Potassium, N-acetyl-DL-tryptophan, dan Caprylic acid.

Zat Aktif

Paclitaxel

Zat aktif paclitaxel berbentuk kristal putih atau hampir putih, paclitaxel telah dilakukan karakterisasi sifat umumnya, diantaranya pemerian, morfologi, higroskopisitas, polimorfisme, dan isomer potensial. Paclitaxel memiliki bentuk partikel yang tidak beraturan, dan sebagian berbentuk jarum, paclitaxel memiliki 2 bentuk kristal, molekul paclitaxel memiliki beberapa pusat kiral yang memungkinkan adanya steriomer, paclitaxel bersifat agak hikroskopis.

Paclitaxel yang digunakan diperoleh dari 7-TES baccatin III dan N-benzoyl-O-EE-azetidinone (in short azetidinone) sebagai bahan awal dan diproses melakui 2 tahap proses reaksi. Telah dilakukan kontrol terhadap tahapan kritis dan intermediate kritikal selama proses sintesa.

Struktur kimia Paclitaxel telah ditunjukkan berdasarkan uji *elemental analysis, mass spectrometry (MS), nuclear Magnetic Resonance (^{1}H dan ^{13}C) Spectrometry, infrared spectroscopy (IR), UC Spectroscopy, elemental analysis, X-Ray Powder diffraction (XRPD).*

Spesifikasi zat aktif telah ditetapkan terdiri dari deskripsi (visual), kelarutan, identifikasi (IR, HPLC), rotasi spesifik, logam berat, senyawa sejenis (HPLC), sisa pijar, kandungan air, endotoksin bakteri, dan uji mikroba yang ditetapkan berdasarkan kompendia.
Uji stabilitas zat aktif telah dilakukan dan menunjukkan zat aktif stabil ketika disimpan di suhu 25°C dan 30°C selama 36 bulan. Tidak ada informasi uji stabilitas *force degradation* yang dilakukan.

Obat Jadi

Obat jadi diproduksi dalam bentuk serbuk injeksi liofilisasi, dimana paclitaxel diberikan zat tambahan larutan albumin manusia sehingga membentuk ikatan (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)). Proses pembuatan obat dilakukan dengan aseptis dan dilakukan filtrasi dimulai dari dispensing zat aktif dan zat tambahan, pelarutan zat aktif dalam larutan, penambahan larutan albumin manusia, penyiapan *crude emulsion*, homogenisasi, filtrasi, filling, liofilisasi, dan penyegelan. 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. Hasil validasi proses menunjukkan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu deskripsi sebelum dan setelah rekonstitusi, identifikasi (HPLC dan UV), waktu rekonstitusi, pH (setelah rekonstitusi), osmolalitas, kadar air, ukuran partikel, keseragaman bobot, kadar paclitaxel (HPLC), kadar albumin (HPLC), senyawa sejenis (HPLC), sisa pelarut (GC), bahan partikulat, endotoksin baketri, sterilitas, dan uji kebocoran. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets, data stabilitas jangka panjang, ketentuan umum

kompendia, dan pedoman yang berlaku. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dipercepat (40 °C/ RH 75 %) selama 6 bulan dan stabilitas jangka panjang (30°C/75% RH) obat jadi selama 12 bulan dengan hasil memenuhi persyaratan. Obat dapat disetujui hingga shelf life yang diajukan selama 24 bulan pada suhu di bawah 30°C, Lindungi Dari Cahaya|Jauhkan Dari Jangkauan Anak-Anak.

Kesimpulan
Dari aspek mutu, PacliALL serbuk injeksi liofiliasi dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

1. Studi ikatan paclitaxel terikat protein dengan HSA (human serum albumin), mikrotubulus dan sel endotel pembuluh darah dan umbilikus menunjukkan afinitas ikatan yang 2,3; 4,0; 9,9; dan 2,9 kali lipat lebih tinggi dibanding paclitaxel berbasis pelarut.
2. Pada tikus jantan, terdapat peningkatan AUC dan Cmax bersama dengan peningkatan dosis paclitaxel yang terikat protein. Tmax sebesar 0,03 jam dengan waktu paruh bervariasi mulai 19 jam (dosis 5 mg/kg) sampai 8,48 jam (dosis 116,7 mg/kg). Pada manusia, waktu paruh berkisar antara 11,7-27,4 jam.
3. Metabolisme dan ekskresi partikel paclitaxel yang terikat protein serupa dengan yang berbasis pelarut.
4. Studi toksisitas dosis tunggal pada mencit jantan dengan follow-up selama 28 hari menunjukkan LD50 447 mg/kg pada paclitaxel yang terikat protein dan 7,5 mg/kg pada paclitaxel berbasis pelarut.
5. Pada toksisitas dosis berulang pada mencit, pada pemberian paclitaxel yang terikat protein selama 5 hari dan diikuti selama 28 hari, tidak terjadi kematian pada dosis 30 mg/kg, 1 kematian pada dosis 69 mg/kg dan semua mati pada dosis 103 mg/kg. Pada paclitaxel berbasis pelarut, terdapat 1 dan 2 kematian pada dosis 6 dan 9 mg/kg, dan semua mati pada dosis ≥ 13,4 mg/kg. LD50 didapatkan sebesar 76,2 mg/kg untuk paclitaxel yang terikat protein dan 8,1 mg/kg untuk paclitaxel yang berbasis pelarut.
    a. Pada studi toksisitas dosis berulang pada mencit NCr-nu betina atimik selama 5 hari, didapatkan LD10 < 45 mg/kg/hari, baik untuk paclitaxel yang terikat protein dan paclitaxel berbasis pelarut. Tidak ada kematian pada mencit yang mendapatkan HSA. Tidak nampak adanya tanda toksisitas yang nyata.
6. Tidak terdapat adanya efek genotoksisitas paclitaxel terikat protein.

Studi Klinik

Data yang diserahkan 5 studi terpublikasi fase I, 2 studi fase I/II, 4 studi fase II dan masing-masing 1 studi terpublikasi untuk tiap indikasi yang diajukan, yaitu Studi fase 3 MBC CA0120 untuk mendukung indikasi *metastatic breast cancer,* Studi fase 3 MPACT CA046 untuk mendukung indikasi *adenocarcinoma of the pancreas,* dan Studi fase 3 NSCLC CA031 untuk mendukung indikasi *advance NSCLC.*

Hasil evaluasi terhadap studi yang diserahkan sebagai berikut:
Efikasi :

1. Studi-studi klinik fase I pada subjek dengan kanker advanced atau metastatik menunjukkan bahwa:
    a. Pada studi dengan subjek yang sebagian besar menderita kanker payudara yang advanced dan gagal dengan terapi standar, diperoleh MTD 150 mg/m^2 per minggu pada yang lightly pretreated atau 100 mg/m^2 per minggu pada yang highly pretreated. Dosis yang direkomendasikan adalah 100 mg/m^2 per minggu.
    b. Pada studi dengan subjek sebagian besar adalah NSCLC maligna yang gagal dengan terapi standar, dosis yang direkomendasikan adalah 260 mg/m^2 setiap 3 minggu.
    c. Cmax paclitaxel terlihat pada akhir pemberian infus, dan penurunannya bersifat bifasik. Cmax paclitaxel terikat protein lebih besar dibanding paclitaxel berbasis pelarut. Peningkatan dosis diikuti dengan peningkatan Cmax dan AUC, dan ini berkorelasi dengan kejadian toksisitas. Nilai t1/2 rerata 15-27 jam, serupa antar dosis.
    d. Toksisitas hematologisnya berupa myelosupresi (neutropenia, anemia, trombositopenia) yang umumnya juga grade ringan.

e. Toksisitas nonhematologis sebagian besar grade 1-2, berupa neuropati perifer, mual, muntah, artralgia, myalgia, fatigue, kulit kering, rash, onikolisis, alopesia. Neuropati perifer bisa diatasi dengan penurunan dosis.

2. Studi-studi klinik fase II pada subjek dengan kanker advanced atau metastatik menunjukkan bahwa:
   a. Hasil studi MPACT CA040 yang membandingkan penggunaan nab-paclitaxel pada dosis 100, 125, dan 150 mg/m^2 pada pasien metastatic adenocarcinoma menunjukkan bahwa pada dosis 125 mg/m^2 (44 pasien), median PFS adalah 7,9 bulan (95%CI 5,8-11), median OS 12,2 bulan (95%CI 8,9-17,9), dan 1-year survival 48%. RR sebesar 46% untuk keseluruhan pasien. Pada dosis 100 dan 125 mg mg/m^2 didapatkan ORR sebesar 45% dan 48%, dengan DCR sebesar 60% dan 68%.
   b. Hasil studi MBC CA0020 yang menilai penggunaan nab-paclitaxel pada dosis 300 mg/m^2 pada pasien *metastatic breast cancer* menunjukkan pasien mendapatkan sebanyak median 6 siklus. Sebanyak 25% pasien mengalami penurunan dosis terutama karena toksisitas hematologis. Sebagian besar ditunda selama 4-8 hari. ORR sebesar 48% (95%CI 35,3-60). CR dilaporkan pada 2 pasien dan PR pada 28 pasien. Respon maksimum dilaporkan paling sering pada siklus 2 dan 4. Response rate lebih tinggi pada pasien yang treatment-naive untuk penyakit metastatiknya (64% vs 21%). Respon juga lebih tinggi pada pasien tanpa paparan sebelumnya terhadap anthracycline (58% vs 41%). Response rate pada pasien dengan lokasi lesi dominan di viseral adalah 40% dan yang nonviseral sebesar 68%
   c. Hasil studi MBC CA0020 OLD yang menilai penggunaan nab-paclitaxel pada dosis 175 mg/m^2 pada pasien *metastatic breast cancer* menujukkan ORR 41% (95%CI 17,8-64,5), CBR 47% (95%CI 23,3-70,8), median PFS 23 minggu (95%CI 15,7-30,3), dan median OS 79 minggu.
   d. Hasil studi NSCLC CA018 yang menilai penggunaan nab-paclitaxel pada dosis 260 mg/m^2 tiap tiga minggu pada pasien NSCLC menunjukkan ORR sebesar 16,3% (95%CI 5,24-27,31), semua responnya berupa PR; DCR sebesar 48,8% (95%CI 33,9-63,78%). Sebanyak 79% pasien telah megalami progresi; dan Median TTP 6 bulan (95%CI 3,9-6,5), median OS 11 bulan (95%CI 9,5-16,2).
   e. Hasil studi NSCLC CA018 yang menilai penggunaan nab-paclitaxel pada dosis 80-200 mg/m2 pada hari 1, 8 dan 15 dalam siklus 28 harian pada pasien NSCLC menunjukkan ORR 30% (95%CI 16-44); SD selama ≥ 16 minggu terlihat pada 20% pasien, dengan penurunan terbesar ukuran tumor berkisar antara 3-27%. DCR 50% (95%CI 35-66); median time to progression 5 bulan (96% VI 3-8). Median OS 11 bulan (95%CI 7-NR). One-year survival adalah 41%.
   f. Hasil studi NSCLC CA018 pada pasien dengan advanced NSCLC menunjukkan tidak nampak adanya hubungan dose proportionality pada ORR dan DCR, baik untuk yang dosis 3 mingguan maupun mingguan.

3. Studi fase 3 MBC CA0120 membandingkan pemberian nab-paclitaxel 260 mg/m^2 IV selama 30 menit, 3 minggu sekali (n = 229 subjek) dengan pemberian Paclitaxel standar 175 mg/m^2 IV selama 3 jam, 3 minggu sekali (n = 225 subjek) pada pasien wanita dewasa yang mengalami *metastatic breast cancer.* Hasil studi menunjukkan:
   - *Overall Response Rate* (ORR) lebih besar secara signifikan pada pasien yang menerima nab-paclitaxel dibandingkan paclitaxel standar untuk keseluruhan pasien (33% vs 19%, p = 0,001), ORR pada pasien yang mendapat terapi lini pertama (n = 97 vs 89) adalah 42% vs 27%, p = 0,029, sedangkan pada pasien yang mendapat terapi lini kedua atau lebih (n = 132 vs 136) adalah 27% vs 13%, p = 0,006, dan pada pasien yang sudah mendapat *anthracycline* pada *setting* ajuvan dan/metastatik (34% vs 18%, p = 0,002) dan pada *setting* metastatik saja (27% vs 14%, p = 0,010)
   - Median *Time to progression (TTP)* keseluruhan pasien adalah 23 minggu vs 16,9 minggu (HR 0,75; p = 0,006). Median TTP pada pasien yang mendapat terapi lini pertama adalah 24 vs 19,7 minggu (tidak bermakna), sedangkan pada pasien yang mendapat terapi lini kedua atau lebih adalah 20,9 vs 16,1 minggu (HR 0,73, p = 0,020).
   - Median *Overall Survival (OS)* keseluruhan pasien adalah 65 vs 55,7 minggu (p = 0,374). Median OS pada pasien yang mendapat lini pertama tidak berbeda bermakna, sedangkan pada pasien yang mendapat terapi lini kedua atau lebih berbeda bermakna yaitu : 56,4 vs 46,7 minggu (HR 0,73, p = 0,024).

4. Studi fase 3 MPACT CA046 membandingkan pemberian Nab-paclitaxel 125 mg/m2 IV + gemcitabine 1000 mg/m2 IV pada hari 1, 8, 15, 29, 36, 43 dalam siklus 8 minggu (siklus 1) lalu pada hari 1, 8, dan 15 tiap 4 minggu untuk siklus-siklus berikutnya (n = 431 subjek) dengan pemberian gemcitabine 1000 mg/m2 IV per minggu selama 7 minggu dalam siklus 8 minggu (siklus 1) lalu selama 3 minggu pertama siklus 4 mingguan untuk siklus-siklus berikutnya. (n = 430 subjek) pada pasien dewasa yang mengalami metastatic adenocarcinoma of the pancreas. Hasil studi menunjukkan terdapat perbedaan signifikan efikasi penggunaan nabpaclitaxel + gemcitabine vs gemcitabine dalam hal Overall Survival (OS), Progression Free Survival (PFS), Time to Treatment Failure, Overall Response Rate (ORR), dan Disease Control Rate (DCR)pada pasien adenokarsinoma pankreas metastatik yang belum diterapi sebelumnya.
    - Median OS adalah 8,5 vs 6,7 bulan (HR 0,72, 95%CI 0,62-0,83, p < 0,001). Pada 12 bulan, OS-nya 35% vs 22% (p < 0,001); dan pada 24 bulan OS-nya 9% vs 4% (p = 0,02).
    - Median PFS menurut penilaian independen adalah 5,5 vs 3,7 bulan (HR 0,69; 95%CI 0,58-0,82, p < 0,001) dan PFS rate pada 12 bulan adalah 16% vs 9%. Median PFS menurut penilaian peneliti adalah 5,3 vs 3,5 bulan (HR 0,61, 95%CI 0,52-0,71, p < 0,001).
    - Median time to treatment failureadalah 5,1 vs 3,6 bulan (HR 0,70, 95%CI 0,60-0,80, p < 0,001).
    - ORR menurut penilaian independen adalah 23% vs 7% (HR 3,19, 95%CI 2,18-4,66, p < 0,001). ORR menurut penilaian peneliti adalah 29% vs 8% (HR 3,81, 95%CI 2,66-5,46, p < 0,001).
    - DCR 48% vs 33% (HR 1,46, 95%CI 1,23-1,72, p < 0,001).

5. Studi fase 3 NSCLC CA031 membandingkan pemberian nab-paclitaxel 100 mg/m^2 Infus IV selama 30 menit pada hari 1, 8 dan 15 (n = 521 subjek) dengan pemberian Paclitaxel standar 200 mg/m^2 IV selama 3 jam (n = 531 subjek), masing-masing dalam kombinasi dengan carboplatin pada pasien *non resectable stage IIIb or stage IV Non-Small Cell Lung Cancer (NSCLC), Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1* yang sebelumnya belum mendapat terapi dan tidak diberikan radioterapi dalam waktu 4 minggu penelitian. Hasil studi menunjukkan:
    - ORR lebih besar secara bermakna pada pasien yang menerima nab-paclitaxel dibandingkan paclitaxel standar yaitu 33% vs 25%, *response rate ratio* 1,31 (95%CI 1,082-1,593, p = 0,005).
    - Tidak terdapat peningkatan PFS yang bermakna pada pemberian nab paclitaxel vs paclitaxel standard (median PFS 6,3 bulan vs 5,8 bulan) dan median OS 12,1 bulan vs 11,2 bulan

Keamanan:

1. Studi fase 3 MBC CA0120 menunjukkan hasil keamanan:
    - Profil keamanan pada pasien yang mendapat nab-paclitaxel vs paclitaxel standar sebanding. Tidak terdapat kematian yang terkait dengan pengobatan pada kedua kelompok
    - Pada kelompok pasien yang berusia > 65 tahun, insidensi Adverse Event (AE) seperti neutropenia, leukopenia, mual, hiperglikemia, dan flushing lebih rendah pada kelompok nab-paclitaxel.
    - Tidak terdapat kematian yang terkait dengan pengobatan pada kedua kelompok

2. Studi fase 3 MPACT CA046 menunjukkan hasil keamanan:
    - AE yang lebih sering ditemui pada kelompok nab-paclitaxel + gemcitabine dibanding kelompok gemcitabine saja adalah netropenia, lekopenia, fatigue, dan neuropati perifer.
    - Tidak ada kejadian Serious Adverse Event (SAE) (50% vs 43%), termasuk kejadian kematian (4% vs 4%) dengan AE grade ≥ 3 yang lebih banyak terjadi pada kelompok nab-paclitaxel+gemcitabine adalah neutropenia, leukopenia, *fatigue,* dan neuropati perifer.
    - AE hematologis grade > 3 yang lebih banyak terjadi pada kelompok nab+paclitaxel+gemcitabine adalah netropenia (38% vs 27%) dan lekopenia (31% vs 16%). Lebih banyak pasien kelompok nab-paclitaxel+gemcitabine yang memperoleh white blood cell growth factors (26% vs 15%)
    - AE non-hematologis grade > 3 yang dialami > 5% pasien yang lebih banyak terjadi pada kelompok nab-paclitaxel+gemcitabine adalah fatigue (17% vs 7%) dan neuropati perifer (17% vs 1%). Insidensi neuropati perifer yang menyebabkan peghentian obat sebesar 8%. Untuk neuropati perifer grade > 3, onset terjadinya lebih lambat pada kelompok nab-paclitaxel dibanding pada kelompok gemcitabine saja dan median waktu perbaikannya ke grade < 1 lebih cepat dibanding kelompok gemcitabine saja. Sebanyak 44% subjek

memulai terapi nab-paclitaxel+gemcitabine kembali dengan dosis lebih rendah dalam median 23 hari sesudah onset neuropati perifer grade > 3.

3. Studi fase 3 NSCLC CA031 menunjukkan hasil keamanan:
   - Penurunan dosis lebih banyak terjadi pada kelompok nab-paclitaxel yaitu 46% vs 23%, terutama disebabkan karena efek samping neutropenia (29% vs 10%), trombositopenia (13% vs 4 %), anemia (6% vs < 1%) dan neuropati sensorik (2% vs 6%)
   - Penundaan dosis lebih sering terjadi pada kelompok nab-paclitaxel yaitu 82% vs 54%
   - Terjadi 2 kematian terkait pengobatan, masing-masing 1 pada tiap kelompok.
4. Tidak ada risiko teridentifikasi yang penting, risiko potensial yang penting, dan informasi yang hilang yang masuk ke dalam daftar pada RMP.

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Untuk meminimalkan risiko keamanan, sinyal keamanan yang teridentifikasi dicantumkan pada informasi produk dan rencana PV yang dilakukan adalah PV rutin.

EVALUASI
Penilaian Manfaat-Risiko

PacliALL merupakan obat dengan zat aktif Paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)). Paclitaxel merupakan inhibitor mikrotubulus yang berperan dalam mempromosikan pembentukan mikrotubulus dari dimer tubulin serta menstabilkan mikrotubulus dengan mencegah depolimerisasi. PacliALL mengandung nanopartikel albumin manusia-paclitaxel, di mana paclitaxel berada dalam bentuk non-kristalin (amorfa). Setelah pemberian secara intravena, nanopartikel tersebut dengan cepat terdisosiasi menjadi kompleks paclitaxel yang terikat albumin. Kanker payudara, kanker paru NSCLC, dan adenokarsinoma pankreas adalah bentuk kanker paling umum terjadi, termasuk di Indonesia.

Berdasarkan data mutu yang telah dievaluasi, produksi zat aktif dan produk jadi PacliALL telah dikontrol dengan baik mulai dari bahan baku, proses pembuatan, hingga tahap akhir sehingga dapat menghasilkan produk yang memenuhi spesifikasi pelulusan dan *shelf-life*. Data stabilitas yang tersedia mendukung stabilitas obat pada penyimpanan selama 24 bulan pada suhu di bawah 30°C.

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

a. Aspek yang menguntungkan:
   - Albumin diketahui memediasi transitosis caveola endotel terhadap komponen plasma, dan studi in vitro menunjukkan bahwa keberadaan albumin dalam PacliALL meningkatkan transportasi paclitaxel melintasi sel endotel.
   - Hasil Studi fase 3 MBC CA0120 (n=454) menunjukkan bahwa pemberian nab-paclitaxel pada pasien wanita dewasa yang mengalami *metastatic breast cancer* meningkatkan ORR, median TTP, dan median OS dibandingkan paclitaxel standar.
   - Hasil studi MPACT CA046 (n=861) menunjukkan bahwa pemberian Nab-paclitaxel IV + gemcitabine IV pada pada pasien dewasa yang mengalami *metastatic adenocarcinoma of the pancreas* meningkatkan median OS, PFS, TTP, dan ORR dibandingkan dengan gemcitabine IV.
   - Hasil studi NSCLC CA031 (n=1052) pemberian nab-paclitaxel+carboplatin pada pasien *non resectable stage IIIb or stage IV Non-Small Cell Lung Cancer (NSCLC) meningkatkan ORR* dibandingkan dengan pemberian Paclitaxel+carboplatin

b. Aspek yang tidak menguntungkan:
   - AE yang sering ditemukan di semua studi adalah neutropenia, AE lainnya adalah mual, leukopenia, *fatigue,* neuropati perifer, anemia, trombositopenia.
   - Profil keamanan pada pasien yang mendapat nab-paclitaxel vs paclitaxel standar sebanding

Kesimpulan Manfaat-Risiko

Secara keseluruhan obat ini menunjukkan kemanfaatan penggunaan nab-paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)) pada pasien *metastatic breast cancer, adenocarcinoma of the pancreas, dan advance NSCLC.* Risiko efek samping termasuk efek

samping serius perlu dikomunikasikan dan dicantumkan dalam Informasi Produk.

KEPUTUSAN

Berdasarkan hal-hal tersebut di atas PacliALL serbuk injeksi liofilisasi diterima dengan indikasi sebagai berikut:

Indikasi:

1. Metastatic Breast Cancer
PacliALL is indicated for the treatment of metastatic breast cancer after failure of firstline treatment for metastatic disease. Prior therapy should have included an anthracycline unless clinically contraindicated.
2. Non-Small Cell Lung Cancer
PacliALL is indicated for the first line-line treatment locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
3. Adenocarcinoma of The Pancreas
PacliALL is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

dengan ketentuan 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
PACLIALL

PRODUCT INFORMATION

Drug name	:	PacliALL
Dosage form	:	Lyophilized Injection Powder
Active ingredient	:	Each vial contains: Paclitaxel 100 mg (Paclitaxel Bound Albumin)
Packaging	:	Box, 1 vial @ 100 mg
Registrant	:	PT. Soho Industri Farmasi
Manufacturer	:	Panacea Biotec Pharma Ltd., Malpur, Baddi, Dist. Solan, Himachal Pradesh, 173205, India
Registration Category	:	Registration of new drugs that have been registered with new dosage forms, new indications and posology
Indications that submitted:	:	*1. Metastatic Breast Cancer* *Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.* *2. Non-Small Cell Lung Cancer* *Paclitaxel is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.* *3. Adenocarcinoma of the Pancreas* *Paclitaxel is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.*

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, including in Indonesia. According to GLOBOCAN 2020 data, breast cancer ranks first in Indonesia, with an estimated 65,858 new cases per year, and a death toll of 22,430.

Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, making it the most common type. Lung cancer is the leading cause of cancer death globally and in Indonesia. GLOBOCAN 2020 recorded approximately 34,783 new cases of lung cancer in Indonesia, with a death toll of 30,843. NSCLC is often diagnosed at an advanced stage.

Pancreatic adenocarcinoma is the most common form of pancreatic cancer, accounting for over 90% of cases. This disease is known for its very poor prognosis and high mortality rate, with a 5-year survival rate of less than 10%. This is because most cases are diagnosed at an advanced stage, when surgery is no longer possible. Globally, according to GLOBOCAN 2020, there were over 495,000 new cases of pancreatic cancer and approximately 466,000 deaths.

PacliALL lyophilized powder is a drug with a new dosage form, new indications and posology, the evaluation is focused on the evaluation of clinical data and drug quality to further prove the efficacy, safety, and quality of the drug. PacliALL is a drug containing the active substance Paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)) with a strength of 100 mg. Paclitaxel is attached to human albumin, in the form of small particles known as nanoparticles. Paclitaxel is included in m the taxanes drug group used in cancer treatment.

Paclitaxel is a microtubule inhibitor that promotes microtubule formation from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stabilization inhibits the normal dynamic reorganization of the microtubule network, which is essential for cellular function during interphase and mitosis. Paclitaxel induces the formation of abnormal arrangements, or "bundles," of microtubules throughout the cell cycle, as well as the formation of multiple microtubule asters

during mitosis.

PacliALL contains human albumin-paclitaxel nanoparticles, where paclitaxel is in a non-crystalline (amorphous) form. After intravenous administration, these nanoparticles rapidly dissociate into albumin-bound paclitaxel complexes. Albumin is known to mediate endothelial caveolae transitosis of plasma components, and in vitro studies have shown that the presence of albumin in PacliALL enhances paclitaxel transport across endothelial cells.

Considering that PacliALL injection powder is a drug with a new dosage form, strength, indication and posology, the evaluation is focused on evaluating non-clinical and clinical data and drug quality to further prove the drug's efficacy, safety and quality.

QUALITY ASPECT

PacliALL is a medication containing the active ingredient paclitaxel. This medication contains albumin, which binds to paclitaxel and helps it dissolve in the blood and penetrate blood vessel walls to the tumor. The albumin used is a 25% human albumin solution containing additional ingredients such as sodium, potassium, N-acetyl-DL-tryptophan, and caprylic acid.

Active Ingredients

Paclitaxel

The active ingredient paclitaxel is in the form of white or almost white crystals, paclitaxel has been characterized for its general properties, including appearance, morphology, hygroscopicity, polymorphism, and potential isomers. Paclitaxel has an irregular particle shape, and some are needle-shaped, paclitaxel has 2 crystal forms, paclitaxel molecules have several chiral centers that allow for the existence of steriomers, paclitaxel is hygroscopic.

The paclitaxel used was obtained from 7-TES baccatin III and N-benzoyl-O-EE-azetidinone (abbreviated as azetidinone) as starting materials and processed through a two-step reaction process. Critical steps and critical intermediates were controlled during the synthesis process.

The chemical structure of Paclitaxel has been demonstrated based on *elemental analysis, mass spectrometry (MS), nuclear Magnetic Resonance (^{1}H and ^{13}C) Spectrometry, infrared spectroscopy (IR), UC Spectroscopy, elemental analysis, X-Ray Powder diffraction (XRPD).*

The specifications of the active ingredient have been determined consisting of description (visual), solubility, identification (IR, HPLC), specific rotation, heavy metals, related substance (HPLC), residue on ignition, water content, bacterial endotoxins, and microbial tests determined based on compendia.

Stability testing of the active ingredient has been conducted and shows that the active ingredient is stable when stored at 25°C and 30°C for 36 months. There is no information on *force degradation stability testing* carried out.

Finished product

The finished product is produced in the form of lyophilized injection powder, where paclitaxel is given an additional substance of human albumin solution to form a bond (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)). The drug manufacturing process is carried out aseptically and filtration is carried out starting from dispensing the active substance and additional substances, dissolving the active substance in the solution, adding the human albumin solution, preparing *the crude emulsion*, homogenization, filtration, filling, lyophilization, and sealing. Critical stages have been identified, including *in-process controls* carried out at each stage. Process validation has been carried out on 3 commercial scale batches. The results of the process validation show the process ability to produce a finished product that meet the specified acceptance criteria.

The drug specifications have been established, which are appearance before and after reconstitution, identification (HPLC and UV), reconstitution time, pH (after reconstitution), osmolality, water content, particle size, weight uniformity, paclitaxel content (HPLC), albumin content (HPLC), similar compounds (HPLC), residual solvent (GC), particulate matter, bacterial endotoxin, sterility, and leak test. Parameters in the specifications are selected based on the physicochemical characteristics and critical properties of the active substance by considering, among others, the results of batch tests, long-term stability data, general provisions of the compendia, and applicable guidelines. The analytical method used has been validated. The results of the batch analysis provide results that meet the required specifications.

Accelerated stability data (40°C/75% RH) for 6 months and long-term stability (30°C/75% RH) of the

finished drug for 12 months with results meeting the requirements. The drug can be approved up to the proposed shelf life of 24 months at temperatures below 30°C Protect from Light | Keep Out of Reach of Children.

Conclusion
From the quality aspect, PacliALL lyophilized injection powder can be considered acceptable.

EFFICACY AND SAFETY ASPECTS

Non-Clinical Studies

1. Binding studies of protein-bound paclitaxel with HSA (human serum albumin), microtubules and vascular and umbilical endothelial cells showed binding affinities that were 2.3; 4.0; 9.9; and 2.9-fold higher than solvent-based paclitaxel.
2. In male rats, there was an increase in AUC and Cmax with increasing doses of protein-bound paclitaxel. The Tmax was 0.03 hours, with a half-life varying from 19 hours (5 mg/kg dose) to 8.48 hours (116.7 mg/kg dose). In humans, the half-life ranges from 11.7 to 27.4 hours.
3. The metabolism and excretion of protein-bound paclitaxel particles are similar to those of solvent-based ones.
4. Single dose toxicity studies in male mice with a 28-day follow-up showed an LD50 of 447 mg/kg for protein-bound paclitaxel and 7.5 mg/kg for solvent-based paclitaxel.
5. In repeated dose toxicity studies in mice, when protein-bound paclitaxel was administered for 5 days and followed by 28 days, no deaths occurred at a dose of 30 mg/kg, 1 death at a dose of 69 mg/kg, and all deaths at a dose of 103 mg/kg. In solvent-based paclitaxel, there were 1 and 2 deaths at doses of 6 and 9 mg/kg, respectively, and all deaths at doses ≥ 13.4 mg/kg. The LD50 was 76.2 mg/kg for protein-bound paclitaxel and 8.1 mg/kg for solvent-based paclitaxel.
    a. In a repeated-dose toxicity study in a female NCr-nu mice over 5 days, an LD10 of <45 mg/kg/day was found for both protein-bound and solvent-based paclitaxel. There were no deaths in mice receiving HSA. No obvious signs of toxicity were observed.
6. There was no genotoxic effect of protein-bound paclitaxel.

Clinical Studies

Data submitted were 5 published studies of phase I studies, 2 phase I/II studies, 4 phase II studies and one published study each for each proposed indication, which are the MBC CA0120 phase 3 study to support the indication of *metastatic breast cancer,* the phase 3 MPACT CA046 study to supports the indication *for adenocarcinoma of the pancreas, and* the phase 3 NSCLC CA031 study to supports the indication *for advanced NSCLC.*

The results of the evaluation of the submitted studies are as follows.
Efficacy:

1. Phase I clinical studies in subjects with advanced or metastatic cancer showed that:
    a. In studies involving subjects who mostly had advanced breast cancer and had failed standard therapy, the MTD was 150 mg/m^2 per week in lightly pretreated subjects or 100 mg/m2 ^{per} week in highly pretreated subjects. The recommended dose is 100 mg/m2 ^{per} week.
    b. In studies with subjects mostly malignant NSCLC who failed standard therapy, the recommended dose is 260 mg/m^2 every 3 weeks.
    c. Paclitaxel Cmax is seen at the end of the infusion, and the decline is biphasic. Protein-bound paclitaxel Cmax is greater than solvent-based paclitaxel. Dose increases are accompanied by increases in Cmax and AUC, and these correlate with toxicity. The mean t1/2 is 15–27 hours, similar across doses.
    d. Hematological toxicity is in the form of myelosuppression (neutropenia, anemia, thrombocytopenia) which is generally also mild.
    e. Non-hematologic toxicities were mostly grade 1-2, including peripheral neuropathy, nausea, vomiting, arthralgia, myalgia, fatigue, dry skin, rash, onycholysis, and alopecia. Peripheral neuropathy can be managed by reducing the dose.
2. Phase II clinical studies in subjects with advanced or metastatic cancer showed that:
    a. The results of the MPACT CA040 study comparing the use of nab-paclitaxel at doses of 100, 125, and 150 mg/m^2 in patients with metastatic adenocarcinoma showed that at a dose of 125 mg/m^2 (44 patients), the median PFS was 7.9 months (95%CI 5.8-11), median OS 12.2 months (95%CI 8.9-17.9), and 1-year survival 48%. The RR was 46% for all

patients. At doses of 100 and 125 mg mg/m2, the ORR was 45% and 48%, respectively, with DCR of 60% and 68%.

b. Results from the MBC CA0020 study, which evaluated the use of nab-paclitaxel at a dose of 300 mg/m^2 in *metastatic breast cancer patients*, showed that patients received a median of 6 cycles. Twenty-five percent of patients experienced dose reductions, primarily due to hematologic toxicity. Most of these were delayed for 4–8 days. The ORR was 48% (95%CI 35.3–60). CR was reported in 2 patients and PR in 28 patients. Maximum response was reported most frequently in cycles 2 and 4. Response rates were higher in patients who were treatment-naive for their metastatic disease (64% vs. 21%). Responses were also higher in patients without prior exposure to anthracyclines (58% vs. 41%). Response rates in patients with predominantly visceral lesions were 40% and in non-visceral patients 68%.
c. The results of the MBC CA0020 OLD study, which assessed the use of nab-paclitaxel at a dose of 175 mg/m^2 in patients with *metastatic breast cancer,* showed ORR 41% (95%CI 17.8-64.5), CBR 47% (95%CI 23.3-70.8), median PFS 23 weeks (95%CI 15.7-30.3), and median OS 79 weeks.
d. The results of the NSCLC CA018 study, which assessed the use of nab-paclitaxel at a dose of 260 mg/m^2 every three weeks in NSCLC patients, showed an ORR of 16.3% (95%CI 5.24-27.31), with all responses being PR; DCR of 48.8% (95%CI 33.9-63.78%). 79% of patients had experienced progression; and a median TTP of 6 months (95%CI 3.9-6.5), a median OS of 11 months (95%CI 9.5-16.2).
e. The NSCLC CA018 study, which evaluated the use of nab-paclitaxel at doses of 80-200 mg/m^2 on days 1, 8, and 15 in a 28-day cycle in patients with NSCLC, showed an ORR of 30% (95%CI 16-44); SD for ≥ 16 weeks was seen in 20% of patients, with the largest reduction in tumor size ranging from 3-27%. DCR 50% (95%CI 35-66); median time to progression 5 months (96% VI 3-8). Median OS 11 months (95%CI 7-NR). One-year survival was 41%.
f. The results of the NSCLC CA018 study in patients with advanced NSCLC showed no visible existence the relationship between dose proportionality on ORR and DCR, both for the 3- weekly dose and weekly.

3. The phase 3 MBC CA0120 study compared nab -paclitaxel 260 mg/m^2 IV over 30 minutes, once every 3 weeks (n = 229 subjects) with standard Paclitaxel 175 mg/m^2 IV over 3 hours, once every 3 weeks (n = 225 subjects) in adult female patients with *metastatic breast cancer.* Study results show:
    - *Overall Response Rate* (ORR) was significantly greater in patients receiving nab-paclitaxel compared to standard paclitaxel for all patients (33% vs 19%, p = 0.001), ORR in patients receiving first-line therapy (n = 97 vs 89) is 42% vs 27%, p = 0.029, whereas in patients who received second-line therapy or more (n = 132 vs 136) was 27% vs 13%, p = 0.006, and in patients who had received *anthracycline* in the adjuvant and/or metastatic *setting* (34% vs 18%, p = 0.002) and in metastatic *settings* only (27% vs 14%, p = 0.010)
    - Median *Time to progression The overall TTP was* 23 weeks vs. 16.9 weeks (HR 0.75; p = 0.006). The median *TTP* in patients receiving first-line therapy was 24 vs. 19.7 weeks (not significant), while in patients receiving second-line therapy or more it was 20.9 vs. 16.1 weeks (HR 0.73, p = 0.020).
    - Median *Overall Survival (OS)* for all patients was 65 vs. 55.7 weeks (p = 0.374). Median OS in patients receiving first-line therapy was not significantly different, while in patients receiving second-line therapy or more, it was significantly different: 56.4 vs. 46.7 weeks, HR 0.73, p = 0.024).

4. The phase 3 MPACT CA046 study compared Nab-paclitaxel 125 mg/m^2 IV + gemcitabine 1000 mg/m^2 IV on days 1, 8, 15, 29, 36, and 43 of an 8-week cycle (cycle 1) and then on days 1, 8, and 15 every 4 weeks for subsequent cycles (n = 431 subjects) with gemcitabine 1000 mg/m2 IV weekly for 7 weeks of an 8-week cycle (cycle 1) and then for the first 3 weeks of a 4-week cycle for subsequent cycles (n = 430 subjects) in adult patients with metastatic adenocarcinoma of the pancreas. The study results showed a significant difference in the efficacy of nabpaclitaxel + gemcitabine vs gemcitabine in terms of Overall Survival (OS), Progression Free Survival (PFS), Time to Treatment Failure, Overall Response Rate (ORR), and Disease Control Rate (DCR) in previously untreated metastatic pancreatic adenocarcinoma patients.
    - Median OS was 8.5 vs. 6.7 months (HR 0.72, 95%CI 0.62-0.83, p < 0.001). At 12 months, OS was 35% vs. 22% (p < 0.001); and at 24 months, OS was 9% vs. 4% (p = 0.02).

- Median PFS according to independent assessment was 5.5 vs. 3.7 months (HR 0.69; 95%CI 0.58-0.82, p < 0.001), and PFS rates at 12 months were 16% vs. 9%. Median PFS according to investigator assessment was 5.3 vs. 3.5 months (HR 0.61, 95%CI 0.52-0.71, p < 0.001).
- Median time to treatment failure was 5.1 vs 3.6 months (HR 0.70, 95%CI 0.60-0.80, p < 0.001).
- The ORR according to independent assessment was 23% vs. 7% (HR 3.19, 95%CI 2.18-4.66, p < 0.001). The ORR according to investigator assessment was 29% vs. 8% (HR 3.81, 95%CI 2.66-5.46, p < 0.001).
- DCR 48% vs 33% (HR 1.46, 95%CI 1.23-1.72, p < 0.001).

5. The phase 3 NSCLC study CA031 compared nab-paclitaxel 100 mg/m2 ^{IV} infusion over 30 minutes on days 1, 8, and 15 (n = 521 subjects) with standard Paclitaxel 200 mg/m^2 IV infusion over 3 hours (n = 531 subjects), each in combination with carboplatin in patients with *non-resectable stage IIIb or stage IV Non-Small Cell Lung Cancer (NSCLC), Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1* who had not previously received therapy and had not received radiotherapy within 4 weeks of the study. The study results showed:
   - The ORR was significantly greater in patients receiving nab-paclitaxel compared to standard paclitaxel, namely 33% vs 25%, *response rate ratio* 1.31 (95%CI 1.082-1.593, p = 0.005).
   - There was no significant increase in PFS with nab paclitaxel vs standard paclitaxel (median PFS 6.3 months vs 5.8 months) and median OS 12.1 months vs 11.2 months

Safety:

1. The phase 3 study of MBC CA0120 showed safety results:
   - The safety profile in patients receiving nab-paclitaxel versus standard paclitaxel was comparable. There were no treatment-related deaths in either group.
   - In the group of patients aged > 65 years, the incidence of Adverse Events (AE) such as neutropenia, leukopenia, nausea, hyperglycemia, and flushing was lower in the nab-paclitaxel group.
   - There were no treatment-related deaths in either group.

2. The phase 3 study of MPACT CA046 showed safety results:
   - AEs that were more frequently encountered in the nab-paclitaxel + gemcitabine group compared to the gemcitabine alone group were neutropenia, leukopenia, fatigue, and peripheral neuropathy.
   - There were no Serious Adverse Events (SAE) (50% vs 43%), including death (4% vs 4%) with AE grade ≥ 3 that occurred more frequently in the nab-paclitaxel+gemcitabine group, namely neutropenia, leukopenia , *fatigue,* and peripheral neuropathy.
   - AEs Hematologic Grade > 3 that were more common in the nab+paclitaxel+gemcitabine group were neutropenia (38% vs. 27%) and leukopenia (31% vs. 16%). More patients in the nab-paclitaxel+gemcitabine group received white blood cell growth factors (26% vs. 15%).
   - AEs Non-hematologic Grade > 3 experienced by > 5% of patients and more frequently in the nab-paclitaxel+gemcitabine group were fatigue (17% vs. 7%) and peripheral neuropathy (17% vs. 1%). The incidence of peripheral neuropathy leading to discontinuation was 8%. For peripheral neuropathy grade > 3, the onset was slower in the nab-paclitaxel group than in the gemcitabine-alone group, and the median time to improvement to grade < 1 was faster than in the gemcitabine-alone group. Forty-four percent of subjects restarted nab-paclitaxel+gemcitabine therapy at a lower dose within a median of 23 days after the onset of peripheral neuropathy grade > 3.
3. The phase 3 NSCLC CA031 study showed safety results:
   - Dose reductions were more frequent in the nab-paclitaxel group, which is 46% vs 23%, mainly due to side effects of neutropenia (29% vs 10%), thrombocytopenia (13% vs 4%), anemia (6% vs < 1%) and sensory neuropathy (2% vs 6%)
   - Dose delays were more frequent in the nab-paclitaxel group, namely 82% vs. 54%
   - There were 2 treatment-related deaths, 1 in each group.
4. There are no significant identified risks, significant potential risks, and missing information listed in the RMP.

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

To minimize safety risks, identified safety signals are listed in the product information and the PV plan carried out is routine PV.

EVALUATION
Benefit-Risk Assessment

PacliALL is a drug containing the active ingredient Paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)). Paclitaxel is a microtubule inhibitor that promotes the formation of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. PacliALL contain human albumin nanoparticles -paclitaxel, where paclitaxel is located in non- crystalline (amorphous) form. After administration in a way intravenous, nanoparticles the with fast dissociated become albumin- bound paclitaxel complex. Cancer breast cancer NSCLC, and adenocarcinoma pancreas is form most common cancer happened, including in Indonesia.

Based on evaluated quality data, the production of PacliALL 's active ingredients and finished products is well-controlled, from raw materials through the manufacturing process to the final stage, resulting in a product that meets release and shelf-life specifications. Available stability data supports the drug's stability during storage for 24 months at temperatures below 30°C.

Based on the efficacy and safety data obtained from clinical studies, PacliALL has the following beneficial effects, adverse effects, uncertainties and limitations:

a. Advantageous aspects:
   - Albumin is known to mediate endothelial caveolae transitosis of plasma components, and in vitro studies have shown that the presence of albumin in PacliALL enhances paclitaxel transport across endothelial cells.
   - Study results of the phase 3 MBC CA0120 study (n=454) showed that nab-paclitaxel administration to adult female patients with *metastatic breast cancer* improved ORR, median TTP, and median OS compared to standard paclitaxel.
   - Study results of the MPACT CA046 study (n=861) showed that administration of Nab-paclitaxel IV + gemcitabine IV in adult patients with *metastatic adenocarcinoma of the pancreas* increased median OS, PFS, TTP, and ORR compared with IV gemcitabine.
   - Study results of the NSCLC CA031 study (n=1052) showed that nab-paclitaxel+carboplatin administration in *non-resectable stage IIIb or stage IV Non-Small Cell Lung Cancer (NSCLC) patients increased the ORR compared* to Paclitaxel+carboplatin administration.

b. Unfavorable aspects:
   - The most common AEs found in all studies were neutropenia, other AEs were nausea, leukopenia, *fatigue,* peripheral neuropathy, anemia, thrombocytopenia.
   - The safety profile in patients receiving nab-paclitaxel vs standard paclitaxel was comparable.

Benefit-Risk Conclusion

Overall, this drug demonstrates the efficacy of nab-paclitaxel (Paclitaxel Protein Bound Particles for Injectable Suspension (Albumin Bound)) in patients with *metastatic breast cancer, adenocarcinoma of the pancreas, and advanced NSCLC.* The risk of side effects, including serious side effects, must be communicated and included in the Product Information.

DECISION

Based on the above explanation, PacliALL lyophilized injection powder is accepted with the following indications:

Indications:

1. Metastatic Breast Cancer
PacliALL is indicated for the treatment of metastatic breast cancer after failure of firstline treatment for metastatic disease. Prior therapy should have included an anthracycline unless clinically contraindicated.
2. Non-Small Cell Lung Cancer
PacliALL is indicated for the first line-line treatment locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
3. Adenocarcinoma of The Pancreas
PacliALL iis indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

with provision to periodically submitting Post-Marketing Safety data (Periodic Safety Update Report/PSUR) to the Directorate of Surveillance of Safety, Quality, and Import Export of Drugs, Narcotics, Psychotropics, Precursors, and Addictive Substances (Surveillance Substance Group of Drug Safety Supervision, Narcotics, Psychotropics, and Precursors).