Public Assessment Report
BEVABELL

INFORMASI PRODUK

Nama obat	:	BEVABELL
Bentuk sediaan	:	Larutan Konsentrat Untuk Infus
Zat aktif	:	Bevacizumab 100 mg
Kemasan	:	Dus, 1 vial @ 4 mL
Pendaftar	:	PT CKD OTTO Pharmaceuticals
Produsen	:	TOT Biopharm Co., Ltd, Suzhou, China
Kategori Registrasi	:	Registrasi Produk Biosimilar
Indikasi yang diajukan	:	***Therapeutic Indication(s)*** *Bevabell in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5- fluorouracil/folinic acid/irinotecan is indicated for treatment of patients with metastatic carcinoma of the colon or rectum* ***Metastatic Colorectal Cancer (mCRC)*** *Bevabell in combination with fluropyrimidine–based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.* ***Locally recurrent or metastatic triple negative Breast Cancer (mBC)*** *Bevabell in combination with paclitaxel is indicated for the treatment of patients with locally recurrent or metastatic breast cancer, which is HER-2, estrogen receptor and progesterone receptor negative.* ***Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)*** *Bevabell, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.* ***Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer*** *Bevabell (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for primary adjuvant therapy, of patients with resectable, post-operative, advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, without hypertension.* *Bevabell, in combination with carboplatin and gemcitabine, or in combination with carboplatin and paclitaxel is indicated for the treatment of patients with recurrent, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.* *Bevabell in combination with paclitaxel is indicated for the treatment of patients with recurrent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.* ***Cervical Cancer*** *Bevabell in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic, carcinoma of the cervix.*

Posologi yang diajukan:	:	***Dosage and Administration*** ***General*** *Bevabell should be prepared by a healthcare professional using aseptic technique (see section 4.3 Special Instructions for Use, Handling and Disposal).* *The initial Bevabell dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60- minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.* *Dose reduction of Bevabell for adverse events is not recommended. If indicated, Bevabell should either be permanently discontinued or temporarily suspended as described in section 2.4.1 General, Warnings and Precautions.* ***Metastatic Colorectal Cancer (mCRC)*** *The recommended dose of Bevabell, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarely suspended as described in Special Warnings and Special Precautions for Use.* ***Locally recurrent or metastatic triple negative Breast Cancer (mBC)*** *The recommended dose of Bevabell is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.* *It is recommended that Bevabell treatment be continued until progression of the underlying malignant disease.* ***Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)*** *Bevabell is administered in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by Bevabell as a single agent until disease progression.* *The recommended dose of Bevabell when used in addition to carboplatin–based chemotherapy is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.* ***Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer*** *The recommended dose of Bevabell administered as an intravenous infusion is as follows.* *Front-line treatment:* *15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Bevabell as single agent for 15 months or until disease progression, whichever occurs earlier.* *Treatment of recurrent disease:* *Platinum sensitive:* *15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles followed by continued use of Bevabell as single agent until disease progression.* *Alternatively, 15 mg/kg of body weight every 3 weeks when administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by*

		continued use of Bevabell as single agent until disease progression. *Platinum resistant:* *10 mg/kg body weight given once every 2 weeks when administered in combination with paclitaxel (see section 3.1.2, Clinical/Efficacy Studies, study MO22224 for chemotherapy regimens).* *It is recommended that treatment be continued until disease progression.* ***Cervical Cancer*** *Bevabell is administered in combination with one of the following chemotherapy regimens:* *paclitaxel and cisplatin or paclitaxel and topotecan (see section 3.1.2 study GOG-0240 for further details on the chemotherapy regimens).* *The recommended dose of Bevabell is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion* *It is recommended that Bevabell treatment be continued until progression of the underlying disease.* ***Special Dosage Instructions*** ***Pediatruc use**: The safety and efficacy of Bevabell in patients under the age of 18 years have not been established (see section 2.5.4 Pediatric Use).* ***Geriatric dose**: No dose adjustment is required in the patient ≥ 65 years of age.* ***Renal impairment**: The safety and efficacy of Bevabell have not been studied in patients with renal impairment.* ***Hepatic impairment**: The safety and efficacy of Bevabell have not been studied in patients with hepatic impairment*

PENGANTAR

Bevabell merupakan produk biosimilar yang mengandung Bevacizumab 100mg/4mL. Inovator Bevacizumab yang telah disetujui yaitu Avastin. Evaluasi akan dilakukan menyeluruh terhadap data komparabilitas mutu dan nonklinik dan data klinik untuk memastikan similaritas Bevabell dengan innovator.

ASPEK MUTU

Zat aktif

Bevabell merupakan produk biosimilar yang mengandung zat aktif Bevacizumab 100 mg/4 mL dan memiliki kesetaraan (similaritas) dengan zat aktif inovator berdasarkan parameter mutu, tahapan kritis proses yang telah diidentifikasi, serta kontrol dan rentang penerimaan yang telah ditetapkan. Dokumen terkait proses produksi yang diserahkan bersifat komprehensif dan terperinci.

Obat Jadi

Bevabell diproduksi dan dikemas oleh TOT Biopharm Co., Ltd. Suzhou, China. Proses produksi dari Formulasi sampai dengan Pengemasan serta Quality control dilakukan di fasilitas TOT Biopharm Co., Ltd. Suzhou, China. Proses produksi secara umum terdiri atas *Drug substance pre-filtration, Vial washing, Vial sterilization/ depyrogenation,* ***Sterile filtration, Filling & Stopping, Capping, Visual inspection, Labelling, and Flasking***. Uraian proses produksi diserahkan dengan rincian dan memadai. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan. Validasi terhadap proses produksi telah dilakukan, mencakup proses formulasi, fill finish dan validasi media fill. Hasil validasi menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan. Spesifikasi obat jadi telah ditetapkan, mencakup parameter uji, referensi metode uji serta kriteria penerimaannya. Prosedur uji telah divalidasi. Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang, variabilitas proses produksi maupun metode analisis dan data pengembangan proses yang relevant. Data stabilitas Produk jadi Bevabell mendukung penyimpanan obat jadi selama 24 bulan pada suhu 2℃ - 8°C.

Kesimpulan

Berdasarkan data mutu Bevabell yang diserahkan, produksi zat aktif dan produk jadi telah dikontrol dengan baik mulai dari bahan baku, selama proses pembuatan, hingga tahap akhir sehingga dapat menghasilkan produk obat yang memenuhi spesifikasi pelulusan dan shelf-life, serta menunjukkan kesetaraan (similaritas) mutu dengan produk inovator.

ASPEK KHASIAT KEAMANAN

Data non Klinik

Diserahkan 16 studi nonklinik yaitu:

- Studi penentuan afinitas dan aktivitas ikatan terhadap VEGF 165, VEGF 121 menunjukkan hasil yang sebanding antara obat uji dengan avastin
- Pada data farmakodinamik yang diserahkan, Bevabell dan Avastin menunjukkan hasil yang sebanding dalam
    - Menghambat pertumbuhan xenografts human colon cancer Ls174t pada nude mice (54%-68% vs 56%-62%).
    - Menghambat pertumbuhan xenograft kanker ovarium manusia SK-OV-3 pada nude mice (93%-118% vs 93%-97%).
    - Menghambat pertumbuhan MDA-MB-231 human breast cancer xenografts pada nude mice (47%-69% vs 54%-61%).
    - Menghambat pertumbuhan NCI-H460 human lung cancer xenografts pada nude mice secara (37%-51% vs 32%-54%).
    - Menghambat pertumbuhan U-87MG human malignant glioma xenografts pada nude mice (64%-80% vs 62%-82%).
    - Menghambat pertumbuhan Ls174t human colon cancer xenografts pada nude mice (57% vs 57%).
    - Menghambat pertumbuhan Ls174t human colon cancer xenografts pada nude mice (kombinasi dengan irinotecan) (83% vs 88%).
- Studi farmakokinetik
    - Studi untuk melihat kadar obat di dalam plasma dan jaringan tumor pada *Nude Mice Bearing Ls174t Human Colon Cancer Xenografts* menunjukkan hasil yang terlihat sebanding antara obat uji (Bevabell) dan Avastin dengan hasil waktu untuk mencapai konsentrasi puncak obat uji dan Avastin dalam jaringan tumor adalah 4 jam, dengan konsentrasi puncak masing-masing adalah 3,1µg/ml dan 2,1µg/ml. Tingkat paparan TAB008 dan Avastin dalam plasma nude mice AUC(0-t) masing-masing adalah 4242,9 jam*µg/ml vs 3971,2 jam*µg/ml dan dalam jaringan tumor AUC(0-t) adalah 244,8 jam*ug /ml vs 211,7 jam*µg/ml.
    - Studi pada *Rhesus Monkeys* antara Bevabell vs Avastin pada dosis pemberian 5 mg/kg menunjukkan profil kadar di dalam darah (serum concentration-waktu) yang terlihat

sebanding, dengan nilai Cmax/Cssmax (111,98 ± 12,12) mcg/mL vs (97,80 ± 9,26) mcg/mL (P<0,05) dan AUC0-t (18295,51 ± 1482,57) hr.mcg/mL vs (15113,15 ± 2087,97) hr.mcg/mL (P<0,05)

- Studi toksisitas
  - Pada studi toksisitas tunggal pada tikus ICR dan pada *Cynomolgus Monkeys* , tidak ada toksisitas nyata yang diamati setelah injeksi intravena antibodi monoklonal TAB008 (Bevabell) dan dosis toleransi maksimum (MTD) ≥625 mg/kg pada tikus ICR dan ≥400 mg/kg pada *Cynomolgus Monkeys.*
  - Pada studi toksisitas berulang dosis pemberian 2, 10, 50 mg/kg, pada pengukuran hari ke 1 dan 26, secara keseluruhan Avastin menunjukkan nilai yang lebih tinggi dibanding dengan Bevabell untuk parameter AUC0-72, Cmax dan Tmax
  - Dilaporkan tidak adanya kematian hewan uji pada kedua kelompok uji.
  - Dilaporkan tidak ada toksisitas nyata dan tanda abnormal yang diam.

Data Klinik

Diserahkan studi klinik yaitu:

- 1 studi fase 1 "A Phase I, single dose, randomized, double-blind, parallel controlled study to compare the similarity in pharmacokinetics and safety of TAB008 Monoclonal Antibody Injection versus Avastin® Injection in healthy Chinese male subjects (Study No. TOT-CR-TAB008-I-01)"
- 1 studi fase 3 "A Phase III Clinical Study of TAB008 Monoclonal Antibody Combined with Paclitaxel and Carboplatin Versus Bevacizumab (Avastin®) Combined with Paclitaxel and Carboplatin in the First-line Treatment of Advanced or Recurrent Non-squamous Cell Non-small Cell Lung Cancer (Study No.TOT-CR-TAB008-III-01)".

Hasil evaluasi terhadap studi-studi diatas menunjukkan:

- Hasil studi klinik fase 1 (studi TOT- CR-TAB008-I-01) menunjukkan profil farmakokinetik yang sebanding antara Bevabell dengan Avastin, dengan nilai geometric mean ratio (GMR) sebesar 103,09% (90% CI: 94.69, 112,23) untuk AUC o-∞; 102,65% (90% CI: 94.32, 111.72) untuk AUC 0-t dan 110,77% (90% CI: 103.66, 118.33%) untuk Cmax.
- Hasil studi klinik fase III yang dilakukan pada pasien Advanced or Recurrent Non-squamous Cell Non-small Cell Lung Cancer (n= 549), yang ditunjukkan dengan parameter (FAS):
  - Objective Response Rate (ORR) dalam 6 siklus pengobatan: 55,957% vs 55,720%, rasio ORR yaitu 1.00 dan 90% CI (0.89, 1.14)
  - Disease Control Rate (DCR): 95,703% (245 cases) vs 95,367% (247 cases), rasio 1,00 dengan 90% CI (0,97; 1,04)
  - ORR 2 siklus pengobatan: 50.000% vs 46,718% rasio 1,07 dengan 90% CI (0,92, 1,24)
  - Median Duration of Response (DoR): 245 hari (95% CI: 211, 259) vs 219 hari (95% CI: 189, 255), p = 0,3526
  - Median Progression-Free Survival (PFS): 273 hari (95% CI: 224.00, 299.00) vs 239 hari (95% CI: 225.00, 300.00), HR (95% CI): 0,99 (0,80, 1,22), p= 0.9457
  - One-Year Survival Rate (OSR): 66,21% (95% CI: 59.34, 72.18) vs 68,00% (95% CI: 60.90, 74.09), p=0,6793
  - Median Overall Survival (OS): 611 hari (95% CI: 527.00, 712.00) vs 581 hari (95% CI: 498.00, -), HR (95% CI): 1,06 (0,80, 1,40), p= 0.6549
- Profil Keamanan berdasarkan hasil studi klinik fase 1 menunjukkan jumlah subyek yang mengalami TEAE tampak seimbang antara Bevabell dan Avastin. TEAE terbanyak dilaporkan terkait blood triglycerides increased (5 vs 4), Bilirubin conjugated increased (3 vs 2) dan blood bilirubin unconjugated increased (3 vs 2), epistaxis (3 vs 1) . Tidak ada SAE dan kematian yang dilaporkan
- Profil Keamanan berdasarkan hasil studi fase 3 juga menunjukkan profil keamanan yang sebanding antara Bevabell dan Avastin:

- Total subyek meninggal Bevabell vs Avastin sebanyak 104 (dari 277) subjek vs 92 (dari 271) subyek. Subyek meninggal karena perkembangan penyakit 75 vs 63 subyek dan meninggal selain perkembangan penyakit 29 vs 29 subyek. Penyebab kematian dipertimbangkan not related (78 vs 60 subyek), unlikely related (23 vs 26 subyek), dan possibly related (3 vs 5 subyek).
- Pengamatan imunogenistas menunjukkan kejadian ADA outcome untuk Bevabell vs Avastin sebanyak 3 vs 4 , namun tidak ada yang terkonfirmasi sebagai antibodi netralisasi.

- Risk Management Plan dapat dipertimbangkan:
  - Tidak terdapat informasi *important identified risk*, *important potential risk*, dan *missing information*.
  - Aktivitas farmakovigilans rutin yang dilakukan adalah dengan pelaporan efek samping.
  - Tidak ada rencana aktivitas farmakovigilans tambahan dan rencana studi *post-authorisation.*
  - *Risk minimisation measures* yang dilakukan adalah pencantuman informasi keamanan sesuai produk inovator (Avastin) pada informasi produk.

EVALUASI

Penilaian Manfaat-Risiko

Bevabell merupakan produk biosimilar yang mengandung zat aktif Bevacizumab100mg/4mL. Dokumen terkait proses produksi yang diserahkan telah komperhensif dan terperinci. Tahapan kritis proses telah diidentifikasi dan kontrol beserta rentang penerimaannya telah ditetapkan.

Bevabell terdaftar dengan bentuk sediaan Larutan Konsentrat Untuk Infus. Zat tambahan yang digunakan adalah Sodium Dihydrogen Phosphate Monohydrate, Polysorbate 20, Trehalose Dihydrate, Disodium Hydrogen Phosphate Dodecahydrate dan Water For Injection. Bevabell dikemas dalam Vial dengan 1 besar kemasan, yaitu Dus, 1 Vial @ 4 mL. Obat ini harus disimpan pada suhu dingin (2-8°C). Berdasarkan data mutu yang diserahkan, produksi zat aktif dan produk jadi Bevabell telah dikontrol dengan baik mulai dari bahan baku, selama proses pembuatan, karakterisasi mutu hingga tahap akhir sehingga memastikan bahwa produk obat yang dihasilkan similar dengan obat inovator serta memenuhi spesifikasi pelulusan dan spesifikasi selama shelf-life.

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

a. Aspek yang menguntungkan:
   - Efikasi Bevabell sebanding dengan Avastin berdasarkan hasil studi klinik fase III yang dilakukan pada pasien Advanced or Recurrent Non-squamous Cell Non-small Cell Lung Cancer (n= 549), yang ditunjukkan dengan parameter Objective Response Rate (ORR), Disease Control Rate (DCR), Median Duration of Response (DoR), Median Progression Free Survival (PFS), One Year Survival Rate (OSR), Median Overall Survival (OS).
   - Profil efek samping sebanding dengan Avastin.

b. Aspek yang tidak menguntungkan
   - Adverse drug reactions yang paling banyak dilaporkan yaitu febrile neutropenia. Leucopenia, neutropenia, thrombocytopenia, peripheral sensory neuropathy, hipertensi, diare, nausea, vomiting, asthenia, fatigue.

c. Ketidakpastian dan keterbatasan
   - Belum ada data penggunaan pada
     - Wanita hamil dan menyusui.
     - Anak dan remaja
     - Pasien dengan gangguan hepar dan renal

Kesimpulan evaluasi manfaat-risiko:

Secara keseluruhan obat ini menunjukkan kemanfaatan dalam pengobatan, risiko penggunaan obat minimal, dapat diprediksi dan tidak ada issue keamanan baru dibandingkan dengan inovator.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi produk biosimilar diterima sesuai indikasi dan posologi yang diajukan sebagai berikut:

Indikasi
Therapeutic Indication(s)
Bevabell (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Metastatic Colorectal Cancer (mCRC)
Bevabell in combination with fluropyrimidine–based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Locally recurrent or metastatic triple negative Breast Cancer (mBC)
Bevabell in combination with paclitaxel is indicated for the treatment of patients with locally recurrent or metastatic breast cancer, which is HER-2, estrogen receptor and progesterone receptor negative.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)
Bevabwll, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
Bevabell (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for primary adjuvant therapy, of patients with resectable, post-operative, advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer, without hypertension.
Bevabell, in combination with carboplatin and gemcitabine, or in combination with carboplatin and paclitaxel is indicated for the treatment of patients with recurrent, platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.
Bevabell in combination with paclitaxel is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

Cervical Cancer
Bevabell in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic, carcinoma of the cervix.

Posologi
DOSAGE AND ADMINISTRATION
General
Bevabell should be prepared by a healthcare professional using aseptic technique (see section 4.3 Special Instructions for Use, Handling and Disposal).
The initial Bevabell dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Dose reduction of Bevabell for adverse events is not recommended. If indicated, Bevabell should either be permanently discontinued or temporarily suspended as described in section 2.4.1 General, Warnings and Precautions.

Metastatic Colorectal Cancer (mCRC)

The recommended dose of Bevabell, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarely suspended as described in Special Warnings and Special Precautions for Use.

Locally recurrent or metastatic triple negative Breast Cancer (mBC)
The recommended dose of Bevabell is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.
It is recommended that Bevabell treatment be continued until progression of the underlying malignant disease.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)
Bevabell is administered in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by bevabell as a single agent until disease progression.
The recommended dose of Bevabell when used in addition to carboplatin–based chemotherapy is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
The recommended dose of Bevabell administered as an intravenous infusion is as follows.
Front-line treatment: 15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Bevabell as single agent for 15 months or until disease progression, whichever occurs earlier.
Treatment of recurrent disease: Platinum sensitive:
15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles followed by continued use of Bevabell as single agent until disease progression.
Alternatively, 15 mg/kg of body weight every 3 weeks when administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Bevabell as single agent until disease progression.
Platinum resistant:
10 mg/kg body weight given once every 2 weeks when administered in combination with paclitaxel (see section 3.1.2, study MO22224 for chemotherapy regimens).
It is recommended that treatment be continued until disease progression.

Cervical Cancer
Bevabell is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan (see section 3.1.2 study GOG-0240 for further details on the chemotherapy regimens).
The recommended dose of Bevabell is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.
It is recommended that Bevabell treatment be continued until progression of the underlying disease.

Special Dosage Instructions
***Pediatruc use**: The safety and efficacy of Bevabell in patients under the age of 18 years have not been established (see section 2.5.4 Pediatric Use).*
***Geriatric dose**: No dose adjustment is required in the patient ≥ 65 years of age.*
***Renal impairment**: The safety and efficacy of Bevabell have not been studied in patients with renal impairment.*
***Hepatic impairment**: The safety and efficacy of Bevabell have not been studied in patients with hepatic impairment.*