

INFORMASI PRODUK UNTUK PASIEN

BEVABELL®

Bevacizumab

Larutan Konsentrat Untuk Infus

100 mg/4 mL

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai menggunakan obat ini karena brosur ini berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, diskusikan dengan dokter, apoteker perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat Bagian 4.

Apa yang terdapat di dalam brosur ini:

1. Apa itu Bevabell dan kegunaannya
2. Apa yang perlu Anda ketahui sebelum menggunakan Bevabell
3. Cara penggunaan Bevabell
4. Efek samping yang mungkin terjadi
5. Cara penyimpanan Bevabell
6. Isi kemasan dan informasi lainnya

1. Apa itu Bevabell dan kegunaannya

Bevabell mengandung zat aktif Bevacizumab, suatu antibodi monoclonal *humanized* (sejenis protein yang secara alami dibuat oleh sistem kekebalan untuk membantu pertahanan tubuh terhadap infeksi dan kanker). Bevacizumab secara selektif mengikat protein bernama faktor pertumbuhan endotel vaskular manusia (*human vascular endothelial growth factor*/VEGF), yang ditemukan pada permukaan pembuluh darah dan getah bening dalam tubuh. Protein VEGF menyebabkan pembuluh darah tumbuh di dalam tumor; di mana pembuluh darah ini menyediakan nutrisi dan oksigen untuk tumor tersebut. Ketika Bevacizumab berikatan dengan VEGF, pertumbuhan tumor dicegah dengan menghalangi pertumbuhan pembuluh darah yang menyediakan nutrisi dan oksigen untuk tumor tersebut.

Bevabell adalah obat yang digunakan untuk pasien-pasien dewasa dengan kanker stadium lanjut di usus besar, misalnya di kolon atau dubur (rektum). Bevabell akan diberikan dalam kombinasi dengan obat kemoterapi yang mengandung fluoropirimidin.

Bevabell juga digunakan untuk pasien-pasien dewasa dengan kanker payudara metastatik atau kanker payudara lokal yang berulang, dengan pemeriksaan penanda tumor yang disebut HER-2, reseptor estrogen, dan reseptor progesteron menunjukkan hasil negatif. Pada pasien-pasien tersebut, obat ini akan diberikan bersamaan dengan kemoterapi paclitaxel.

Bevabell juga digunakan dalam pengobatan pasien-pasien dewasa dengan kanker paru-paru non-sel kecil stadium lanjut. Pada pasien ini, Bevabell akan diberikan bersamaan dengan obat kemoterapi lain yaitu carboplatin dan paclitaxel.

Bevabell juga digunakan dalam pengobatan pasien-pasien dewasa dengan kanker epitel ovarium, tuba falopi, atau peritoneum primer stadium lanjut setelah operasi, tanpa adanya hipertensi. Pemberian Bevabell pada pasien-pasien tersebut akan dikombinasikan dengan carboplatin dan paclitaxel.

Ketika digunakan pada pasien-pasien dewasa dengan kanker epitel ovarium, tuba falopi, atau peritoneum primer stadium lanjut yang muncul kembali, dan bersamaan dengan pengobatan kemoterapi platinum. Pemberian Bevabell pada pasien ini akan dikombinasikan dengan carboplatin dan gemcitabine.

2. Apa yang perlu Anda ketahui sebelum menggunakan Bevabell

Jangan menggunakan Bevabell:

- Jika Anda alergi (hipersensitif) terhadap Bevacizumab atau bahan lainnya dalam obat ini (tercantum di Bagian 6).
- Jika Anda alergi (hipersensitif) terhadap produk *Chinese Hamster Ovary Cell* atau antibody monoclonal atau antibody *humanized* lainnya.
- Jika Anda sedang hamil
- Jika Anda menderita sakit susunan saraf pusat metastatik yang tidak terobati

Peringatan dan perhatian

Diskusikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan Bevabell:

- Bevabell dapat meningkatkan risiko pembentukan lubang pada dinding usus. Jika Anda mengalami kondisi-kondisi yang menyebabkan peradangan di dalam perut (misalnya divertikulitis, ulkus lambung, kolitis terkait kemoterapi), mohon mendiskusikannya terlebih dahulu dengan dokter Anda.
- Bevabell dapat meningkatkan risiko terbentuknya hubungan atau saluran abnormal antara dua organ atau pembuluh. Risiko terbentuknya saluran antara vagina dan bagian perut lainnya dapat meningkat jika Anda mengalami kanker serviks persisten, rekuren, atau metastatik.
- Obat ini dapat meningkatkan risiko perdarahan atau gangguan penyembuhan luka pascaoperasi. Jika Anda akan menjalani operasi, baru menjalani operasi besar dalam kurun 28 hari terakhir, atau masih memiliki luka pascaoperasi yang belum sembuh, sebaiknya Anda tidak menggunakan obat ini.
- Bevabell dapat meningkatkan risiko terjadinya infeksi serius pada kulit atau lapisan lebih dalam di bawah kulit, terutama jika Anda memiliki lubang di dinding usus atau gangguan penyembuhan luka.
- Bevabell dapat meningkatkan insidensi tekanan darah tinggi. Jika Anda mengalami tekanan darah tinggi yang tidak terkontrol dengan baik oleh obat-obatan pengendali tekanan darah, mohon konsultasikan dengan dokter Anda mengingat tekanan darah Anda perlu dipastikan terkendali sebelum memulai pengobatan dengan Bevabell.
- Obat ini meningkatkan risiko adanya protein pada air seni Anda terutama jika Anda memiliki tekanan darah tinggi.
- Risiko pembentukan gumpalan darah di arteri (salah satu jenis pembuluh darah) dapat meningkat jika Anda berusia lebih dari 65 tahun, menderita diabetes, atau memiliki riwayat gumpalan darah di arteri sebelumnya. Mohon konsultasikan dengan dokter Anda mengingat gumpalan darah dapat menyebabkan serangan jantung dan stroke.
- Bevabell juga dapat meningkatkan risiko pembentukan gumpalan darah di vena (salah satu jenis pembuluh darah)
- Obat ini dapat menyebabkan perdarahan, terutama perdarahan terkait tumor. Mohon konsultasikan dengan dokter Anda jika Anda atau keluarga Anda memiliki kecenderungan mengalami gangguan perdarahan atau Anda mengonsumsi obat-obatan pengencer darah karena alasan tertentu.

- Bevacell dapat menyebabkan perdarahan di dalam dan sekitar otak. Mohon didiskusikan dengan dokter Anda jika Anda mengalami kanker metastatik yang memengaruhi otak Anda.
- Bevacell dapat meningkatkan risiko perdarahan di paru-paru Anda, termasuk batuk atau meludahkan darah. Mohon diskusikan dengan dokter Anda jika pernah mengalami kondisi ini sebelumnya.
- Bevacell dapat meningkatkan risiko lemah jantung. Penting bagi dokter Anda untuk mengetahui jika Anda pernah mendapat antrasiklin (misalnya doxorubicin, sejenis kemoterapi spesifik yang digunakan untuk mengobati kanker-kanker tertentu) atau menjalani radioterapi untuk dada Anda, atau jika Anda menderita jantung.
- Obat ini dapat menyebabkan infeksi dan menurunnya jumlah neutrofil (salah satu jenis darah yang berperan penting dalam perlindungan terhadap bakteri).
- Bevacell dapat menyebabkan hipersensitivitas (termasuk syok anafilaksis) dan/atau reaksi infus (reaksi terkait penyuntikan obat). Mohon beri tahu dokter, apoteker atau perawat Anda jika Anda pernah mengalami gejala setelah penyuntikan, seperti pusing/perasaan akan pingsan, sesak napas, pembengkakan, atau ruam kulit.
- Suatu efek neurologis yang langka bernama *posterior reversible encephalopathy syndrome* (PRES) diketahui berhubungan dengan terapi Bevacell. Jika Anda mengalami sakit kepala, perubahan penglihatan, kebingungan, atau kejang dengan atau tanpa tekanan darah tinggi, mohon hubungi dokter Anda.

Silakan konsultasikan dengan dokter Anda, meskipun pernyataan-pernyataan di atas hanya pernah Anda alami di masa lampau.

Sebelum Anda mendapat Bevacell atau saat Anda sedang menjalani pengobatan dengan Bevacell:

- Jika Anda sedang atau pernah mengalami nyeri di mulut, gigi, dan/atau rahang, pembengkakan atau seriawan di dalam mulut, rasa baal atau berat pada rahang, atau gigi yang kendur, segera beri tahu dokter dan dokter gigi Anda.
- Jika Anda perlu menjalani prosedur gigi invasif atau operasi gigi, beri tahu dokter gigi Anda bahwa Anda sedang mendapatkan terapi dengan Bevacell, terutama jika Anda juga sedang atau pernah mendapat injeksi bifosfonat ke dalam darah Anda.

Anda mungkin disarankan untuk menjalani pemeriksaan gigi sebelum memulai pengobatan dengan Bevacell.

Anak-anak dan remaja

Penggunaan Bevacell tidak dianjurkan pada anak-anak dan remaja di bawah usia 18 tahun karena keamanan dan manfaatnya belum dapat dipastikan pada kelompok populasi tersebut.

Kematian jaringan tulang (osteonekrosis) pada tulang-tulang selain tulang rahang telah dilaporkan terjadi pada pasien-pasien di bawah usia 18 tahun ketika mendapat pengobatan Bevacell.

Obat-obatan lain dan Bevacell

Sampaikan kepada dokter, apoteker, atau perawat Anda jika Anda sedang mendapat, baru saja mendapat, atau mungkin menggunakan obat-obatan lainnya.

Sampaikan kepada dokter Anda jika Anda sedang mendapat terapi berbasis platinum atau taksan untuk kanker paru-paru atau kanker payudara metastatik. Obat-obatan ini jika diberikan bersamaan dengan Bevacell dapat meningkatkan risiko efek samping yang berat.

Mohon sampaikan kepada dokter Anda jika Anda baru saja mendapat atau sedang menjalani radioterapi.

Kehamilan, menyusui, dan kesuburan

Anda tidak boleh menggunakan obat ini jika Anda sedang hamil. Bevabell dapat menyebabkan gangguan pada janin karena obat ini dapat menghentikan pembentukan pembuluh darah yang baru. Dokter Anda seharusnya menyarankan Anda untuk menggunakan kontrasepsi selama pengobatan dengan Bevabell dan selama setidaknya 6 bulan setelah dosis terakhir Bevabell.

Segera sampaikan secara langsung kepada dokter Anda jika Anda sedang hamil. Menjadi hamil saat sedang menggunakan obat ini, atau sedang merencanakan kehamilan dalam waktu dekat.

Anda tidak boleh menyusui bayi Anda selama mendapatkan pengobatan Bevabell dan selama setidaknya 6 bulan setelah dosis terakhir Bevabell, mengingat obat ini dapat mengganggu pertumbuhan dan perkembangan bayi Anda.

Bevabell dapat mengganggu kesuburan wanita. Untuk informasi selengkapnya, mohon konsultasikan dengan dokter Anda.

Mintalah saran kepada dokter, apoteker, atau perawat Anda sebelum menggunakan obat apa pun.

Kemampuan berkendara dan menggunakan mesin

Bevabell belum terbukti mengurangi kemampuan Anda dalam berkendara atau menggunakan alat-alat atau mesin apapun. Namun, rasa kantuk dan pingsan telah dilaporkan terjadi pada penggunaan Bevabell. Jika Anda mengalami gejala-gejala yang memengaruhi penglihatan atau konsentrasi Anda, atau kemampuan Anda untuk bereaksi, jangan berkendara dan menggunakan mesin sampai gejala tersebut mereda.

3. Cara penggunaan Bevabell**Dosis dan frekuensi pemberian**

Dosis Bevabell yang diperlukan bergantung pada berat badan Anda dan jenis kanker yang perlu diobati. Dosis yang direkomendasikan adalah 5 mg, 7,5 mg, 10 mg, atau 15 mg per kilogram berat badan Anda. Dokter Anda akan meresepkan dosis Bevabell yang sesuai untuk Anda. Anda akan diobati dengan Bevabell setiap 2 atau 3 minggu sekali. Jumlah infus yang Anda terima bergantung pada respons Anda terhadap pengobatan tersebut; sebaiknya Anda melanjutkan pengobatan sampai Bevabell gagal menghentikan pertumbuhan tumor Anda. Dokter Anda akan mendiskusikan hal ini dengan Anda.

Metode dan rute pemberian obat

Bevabell merupakan konsentrat untuk larutan infus. Berdasarkan dosis yang diresepkan untuk Anda, sebagian atau seluruh isi vial Bevabell akan dilarutkan dalam larutan natrium klorida sebelum digunakan. Dokter atau perawat akan diberikan kepada Anda selama 90 menit. Jika dapat ditoleransi dengan baik, infus kedua dapat diberikan selama 60 menit. Infus selanjutnya dapat diberikan kepada Anda dalam waktu 30 menit.

Pemberian Bevabell perlu dihentikan sementara

- Jika Anda mengalami tekanan darah tinggi yang serius dan memerlukan pengobatan dengan obat-obat pengendali tekanan darah,
- Jika Anda mengalami gangguan penyembuhan luka pascaoperasi,
- Jika Anda menjalani operasi.

Pemberian Bevabell perlu dihentikan secara permanen jika Anda mengalami

- Tekanan darah tinggi yang parah dan tidak dapat dikendalikan dengan obat-obatan pengendali tekanan darah; atau peningkatan tekanan darah yang ekstrem secara tiba-tiba,
- Adanya protein dalam air seni Anda disertai dengan pembengkakan pada tubuh Anda,
- Lubang di dinding usus Anda,
- Pembentukan hubungan atau saluran seperti tabung yang abnormal antara tenggorokan dan kerongkongan, antara organ-organ dalam dan kulit, antara vagina dan bagian-bagian usus, atau antara jaringan lainnya yang tidak terhubung secara normal (fistula), dan dinilai sebagai kondisi yang parah oleh dokter Anda,
- Infeksi serius pada kulit atau lapisan-lapisan yang lebih dalam di bawah kulit,
- Gumpalan darah di pembuluh darah arteri Anda,
- Gumpalan darah di pembuluh darah paru-paru Anda,
- Perdarahan berat apapun.

Jika diberikan terlalu banyak Bevacell

- Anda dapat mengalami migrain berat. Jika hal ini terjadi, segera hubungi dokter, apoteker atau perawat Anda,

Jika ada dosis Bevacell yang terlewatkan

- Dokter Anda akan menentukan waktu pemberian dosis Bevacell selanjutnya untuk Anda. Anda perlu mendiskusikan hal ini dengan dokter Anda.

Jika Anda menghentikan pengobatan dengan Bevacell

Penghentian pengobatan dengan Bevacell dapat menghentikan efeknya pada pertumbuhan tumor. Jangan menghentikan pengobatan dengan Bevacell kecuali Anda telah mendiskusikannya dengan dokter Anda.

Jika Anda memiliki pertanyaan-pertanyaan lebih lanjut terkait penggunaan obat ini, konsultasikan kepada dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Jika Anda mengalami efek samping tertentu, sampaikan kepada dokter, apoteker atau perawat Anda. Ini termasuk kemungkinan efek samping lainnya yang tidak tercantum dalam brosur ini.

Efek samping yang tercantum di bawah ini terjadi ketika Bevacell diberikan bersamaan dengan kemoterapi. Ini tidak selalu berarti bahwa efek samping tersebut secara khusus disebabkan oleh Bevacell.

Reaksi alergi

Jika Anda mengalami reaksi alergi, segera beri tahu dokter Anda atau tenaga medis lainnya. Gejala-gejala yang dapat terjadi antara lain: sesak napas atau nyeri dada. Anda juga dapat mengalami kemerahan pada kulit atau ruam, kedinginan dan menggigil, serta rasa mual atau muntah.

Anda perlu langsung mencari pertolongan jika Anda mengalami salah satu dari efek samping berikut.

Efek samping berat yang **sangat umum** (terjadi pada lebih dari 1 dari 10 pasien), antara lain:

- Tekanan darah tinggi,
- Rasa baal atau kesemutan pada tangan atau kaki,

- Penurunan jumlah sel darah, termasuk sel darah putih yang membantu melawan infeksi (hal ini dapat disertai dengan demam), dan sel darah yang membantu penggumpalan darah,
- Rasa lemas dan tidak memiliki energi,
- Rasa lelah,
- Diare, mual, muntah, dan nyeri perut.

Efek samping berat yang **umum** (terjadi pada 1-10 dari 100 pasien), antara lain:

- Perforasi usus,
- Perdarahan, termasuk perdarahan di paru-paru pada pasien kanker paru-paru non-sel kecil,
- Penyumbatan arteri oleh gumpalan darah,
- Penyumbatan vena oleh gumpalan darah,
- Penyumbatan pembuluh darah di paru-paru oleh gumpalan darah,
- Penyumbatan vena di kaki oleh gumpalan darah,
- Gagal jantung,
- Gangguan penyembuhan luka pascaoperasi,
- Kemerahan, pengelupasan, ketidaknyamanan, nyeri, atau melepuh pada jari-jari atau kaki,
- Penurunan jumlah sel darah merah,
- Kekurangan energi,
- Gangguan pada perut dan usus,
- Nyeri otot dan persendian, kelemahan otot,
- Mulut kering disertai rasa haus dan/atau air seni yang sedikit atau berwarna lebih gelap,
- Peradangan pada selaput lendir mulut dan usus, paru-paru dan saluran pernapasan, saluran reproduksi, dan saluran kemih,
- Seriawan di mulut dan saluran dari mulut ke lambung, yang dapat menyebabkan nyeri dan gangguan menelan,
- Nyeri, termasuk sakit kepala, nyeri punggung, dan nyeri di area panggul dan dubur,
- Kumpulan abses yang terlokalisasi,
- Infeksi, dan terutama infeksi darah atau kandung kemih,
- Penurunan suplai darah ke otak atau stroke,
- Rasa kantuk,
- Hidung berdarah (mimisan),
- Peningkatan denyut jantung (nadi),
- Penyumbatan pada usus,
- Hasil uji air seni yang abnormal (adanya protein pada air seni),
- Sesak napas atau kadar oksigen yang rendah di dalam darah,
- Infeksi pada kulit atau lapisan-lapisan yang lebih dalam di bawah kulit,
- Fistula: saluran seperti tabung yang abnormal antara organ-organ dalam dan kulit atau jaringan-jaringan lainnya yang tidak terhubung secara normal, termasuk saluran antara vagina dan usus pada pasien-pasien kanker serviks.
- Reaksi alergi (gejala-gejalanya antara lain sesak napas, wajah memerah, ruam, tekanan darah rendah atau tinggi, kadar oksigen rendah di darah, nyeri dada, atau mual/muntah).
- Reaksi alergi yang tiba-tiba dan parah dengan kesulitan bernapas, bengkak, sakit kepala ringan, detak jantung cepat, berkeringat dan kehilangan kesadaran (syok anafilaksis).

Efek samping berat dengan frekuensi yang **tidak diketahui** (frekuensi tidak dapat diperkirakan dari data yang tersedia) antara lain:

- Infeksi serius pada kulit atau lapisan-lapisan yang lebih dalam di bawah kulit, terutama jika Anda pernah memiliki lubang pada dinding usus atau gangguan penyembuhan luka,
- Reaksi alergi (gejala-gejalanya antara lain sesak napas, wajah memerah, ruam, tekanan darah rendah atau tinggi, kadar oksigen rendah di darah, nyeri dada, atau mual/muntah).

- Efek negatif pada kemampuan wanita untuk memiliki anak (lihat paragraf di bawah daftar efek samping untuk rekomendasi selanjutnya).
- Gangguan otak dengan gejala-gejala seperti kejang, sakit kepala, kebingungan, dan perubahan penglihatan (*Posterior Reversible Encephalopathy Syndrome* atau PRES).
- Gejala-gejala yang menunjukkan perubahan fungsi normal otak (sakit kepala, perubahan penglihatan, kebingungan, atau kejang), dan tekanan darah tinggi,
- Penyumbatan pembuluh darah kapiler di ginjal,
- Tekanan darah tinggi yang abnormal pada pembuluh darah di paru-paru yang menyebabkan sisi kanan jantung bekerja lebih berat dari biasanya,
- Lubang di dinding tulang rawan yang memisahkan kedua lubang hidung,
- Lubang di lambung atau usus,
- Luka terbuka atau lubang di lapisan permukaan lambung atau usus halus (gejala-gejalanya antara lain nyeri perut, rasa kembung, tinja berwarna hitam seperti tar atau darah pada tinja, atau muntah darah), perdarahan dari usus besar bagian bawah,
- Luka pada gusi dengan tulang rahang terbuka yang tidak sembuh dan dapat disertai nyeri dan peradangan jaringan di sekitarnya (lihat paragraf di bawah daftar efek samping untuk rekomendasi selanjutnya),
- Lubang di kandung empedu (tanda dan gejalanya antara lain nyeri perut, demam, dan mual/muntah).

Anda perlu secepatnya mencari pertolongan jika Anda mengalami salah satu dari efek samping berikut.

Efek samping tidak berat yang **sangat umum** (terjadi pada lebih dari 1 dari 10 pasien), antara lain:

- Konstipasi,
- Penurunan nafsu makan,
- Demam,
- Gangguan pada mata (termasuk peningkatan produksi air mata),
- Perubahan cara bicara,
- Perubahan pada indra perasa,
- Hidung berair,
- Kulit kering, pengelupasan dan peradangan kulit, perubahan warna kulit,
- Penurunan berat badan,
- Hidung berdarah (mimisan).

Efek samping tidak berat yang **umum** (terjadi pada 1-10 dari 100 pasien), antara lain:

- Perubahan suara dan suara serak.

Pasien berusia lebih dari 65 tahun memiliki peningkatan risiko efek samping berikut:

- Gumpalan darah di arteri yang menyebabkan stroke atau serangan jantung,
- Penurunan jumlah sel darah putih dan sel darah yang membantu penggumpalan darah,
- Diare,
- Rasa mual,
- Sakit kepala,
- Rasa lelah,
- Tekanan darah tinggi.

Bevabell juga dapat menyebabkan perubahan hasil uji laboratorium yang dilakukan oleh dokter Anda. Hal ini termasuk penurunan jumlah sel darah putih, terutama neutrofil (jenis sel darah putih yang membantu perlindungan terhadap infeksi) dalam darah; adanya protein pada air seni; penurunan kadar kalium, natrium, atau fosfor (suatu mineral) dalam darah; peningkatan kadar kreatinin serum (suatu protein yang diukur kadarnya melalui tes darah

untuk menilai fungsi ginjal); penurunan kadar hemoglobin (ditemukan pada sel darah merah, yang membawa oksigen), yang dapat bersifat parah.

Nyeri pada mulut, gigi, dan/atau rahang, pembengkakan atau luka di dalam mulut, rasa baal berat di rahang, atau gigi kendur. Tanda dan gejala ini dapat menunjukkan adanya kerusakan tulang rahang (osteonekrosis). Langsung sampaikan kepada dokter dan dokter gigi Anda jika Anda mengalami salah satu gejala tersebut.

Wanita pramenopause (wanita yang masih mengalami siklus menstruasi) dapat mengalami siklus menstruasi yang tidak teratur atau terlewatkan dan dapat mengalami gangguan kesuburan. Jika Anda mempertimbangan untuk memiliki anak, sebaiknya Anda mendiskusikan hal ini dengan dokter Anda sebelum pengobatan dimulai.

Bevabell dikembangkan dan dibuat untuk mengobati kanker dengan menyuntikkannya ke dalam aliran darah. Obat ini belum dikembangkan atau dibuat untuk injeksi ke mata. Oleh karena itu, obat ini tidak diperbolehkan untuk digunakan secara demikian. Ketika Bevabell disuntikkan secara langsung ke mata (penggunaan tanpa persetujuan), efek samping berikut dapat terjadi:

- Infeksi atau peradangan pada bola mata,
- Kemerahan pada mata, adanya partikel-partikel kecil atau bintik-bintik dalam pandangan Anda (*floaters*), nyeri mata,
- Adanya kilatan cahaya dengan *floaters*, yang berlanjut ke penurunan penglihatan,
- Peningkatan tekanan di bola mata,
- Perdarahan di mata.

Pelaporan efek samping

Apabila Anda mengalami efek samping apa pun, hubungi dokter, apoteker atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi tambahan terkait keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui:

Farmakovigilans- PT CKD OTTO Pharmaceuticals

Email: cs@ckd-otto.com

Tel: 0811-971-918

Atau

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,

Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Phone: +62-21-4244691 Ext.1079

Website: <https://e-meso.pom.go.id/ADR>

5. Cara penyimpanan Bevabell

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada kemasan luar dan pada label vial setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

Simpan obat ini di lemari pendingin (2 – 8°C).

Jangan dibekukan.

Simpan vial di dalam kemasan luar untuk melindunginya dari cahaya.

Larutan infus harus segera digunakan setelah dilarutkan. Jangan menggunakan Bevabell jika Anda menemukan partikel-partikel tertentu atau perubahan warna sebelum pemberian obat.

Jangan membuang obat melalui saluran limbah cair atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak digunakan. Upaya-upaya ini akan membantu perlindungan lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan Bevabell

- Zat aktif obat ini adalah Bevacizumab. Setiap mL konsentrat mengandung 25 mg Bevacizumab, setara dengan 1,4 – 16,5 mg/mL ketika dilarutkan sesuai rekomendasi.
- Setiap vial 4 mL mengandung 100 mg Bevacizumab, setara dengan 1,4 mg/mL ketika dilarutkan sesuai rekomendasi.
- Bahan-bahan lainnya adalah trehalose dihidrat, sodium dihydrogen phosphate monohydrate, polisorbit 20, disodium hydrogen phosphate dodecahydrate, dan air untuk injeksi.

Tampilan Bevabell serta isi dalam kemasan

Bevabell adalah konsentrat untuk larutan infus. Konsentrat ini merupakan cairan tidak berwarna hingga cokelat muda dan jernih hingga buram di dalam vial kaca dengan tutup karet. Setiap vial mengandung 100 mg Bevacizumab di dalam 4 mL larutan. Setiap kemasan Bevabell mengandung satu vial.

Kemasan

Dus, 1 vial @ 4 mL

No. Reg.: DKlxxxxxxxxxxxxx

Obat: jauhkan dari jangkauan anak-anak
HARUS DENGAN RESEP DOKTER

Diproduksi oleh:

BioDlink Biopharm Co., Ltd.
Suzhou – Cina

Diimpor oleh:

PT CKD OTTO Pharmaceuticals
Bekasi – Indonesia

BEVABELL®

Bevacizumab

Concentrate for Solution for Infusion

100 mg/4 mL

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Anti-neoplastic agent ATC Code: L01FG01

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Colorless to pale brown and clear to opalescent liquid. Sterile liquid for intravenous (IV) infusion. Bevabell is not formulated for intravitreal use (see section 2.4.1 *Warnings and Precautions, General*).

1.4 Sterile/Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: Bevacizumab (humanised anti-VEGF monoclonal antibody).

Bevabell is supplied in 100 mg preservative-free, single-use vials containing 4 mL of bevacizumab (25 mg/mL).

Each Bevabell 100 mg vial contains 100 mg of bevacizumab.

Excipients: trehalose dehydrate, polysorbate 20, sodium dihydrogen phosphate, disodium hydrogen phosphate dodecahydrate, water for injection.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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)

Bevacizumab in combination with fluoropyrimidine-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)

Bevacizumab 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)

Bevacizumab, 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

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.

Bevacizumab, 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.

Bevacizumab 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

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

2.2 Dosage and Administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician. The safety and efficacy of alternating or switching between Bevacizumab and products that are biosimilar but not deemed interchangeable have not been established. Therefore, the benefit-risk of alternating or switching need to be carefully considered.

Bevacizumab should be prepared by a healthcare professional using aseptic technique (see section 4.2 *Special Instructions for Use, Handling and Disposal*).

The initial bevacizumab 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 bevacizumab for adverse events is not recommended. If indicated, bevacizumab should either be permanently discontinued or temporarily suspended as described in section 2.4.1 *General, Warnings and Precautions*.

Bevacizumab is not formulated for intravitreal use (see section 4.2 *Special Instruction for Use, Handling, and Disposal*).

Metastatic Colorectal Cancer (mCRC)

The recommended dose of bevacizumab, 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 temporarily suspended as described in *Warnings and Precautions*.

Locally recurrent or metastatic triple negative Breast Cancer (mBC)

The recommended dose of bevacizumab 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 bevacizumab treatment be continued until progression of the underlying malignant disease.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

Bevacizumab is administered in combination with carboplatin and paclitaxel for up to 6 cycles of treatment followed by bevacizumab as a single agent until disease progression. The recommended dose of bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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 bevacizumab 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

Bevacizumab is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan (see section 3.1.2 *Clinical/Efficacy Studies, study GOG-0240 for further details on the chemotherapy regimens*).

The recommended dose of bevacizumab is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.

It is recommended that bevacizumab treatment be continued until progression of the underlying disease.

2.2.1 Special Dosage Instructions

Pediatric use: The safety and efficacy of bevacizumab in children and adolescents (<18 years) have not been established (see section 2.5.4 *Pediatric Use*).

Geriatric use: No dose adjustment is required in the patient $\geq$ 65 years of age.

Renal impairment: The safety and efficacy of bevacizumab have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of bevacizumab have not been studied in patients with hepatic impairment.

2.3 Contraindications

Bevacizumab is contraindicated in patients with:

- Known hypersensitivity to any components of the product
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanised antibodies
- Pregnancy (see section 2.5 *Use in Special Populations*)
- Untreated Central Nervous System (CNS) metastases (see also sections 2.4 *Warnings and Precautions* and 2.6 *Undesirable Effects*).

2.4 Warnings and Precautions

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal Perforations and Fistula

Patients may be at increased risk for the development of gastrointestinal perforation (see section 2.6.1 *Undesirable Effects, Clinical Trials*) and gallbladder perforation (see section 2.6.2 *Undesirable Effects, Post Marketing*) when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of fistula between the vagina and any part of the GI tract (Gastrointestinal vaginal fistula) (see section 2.6.1 *Undesirable Effects, Clinical Trials, Gastrointestinal Perforations and Fistula*).

Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients.

Non-GI Fistula (see section 2.6.1 Clinical Trials, Undesirable Effects)

Patients may be at increased risk for the development of fistula when treated with bevacizumab (see section 2.6.1. *Undesirable Effects, Clinical Trials, Non-GI Fistula*).

Permanently discontinue bevacizumab in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistula. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Haemorrhage (see section 2.6.1 Undesirable Effects, Clinical Trials)

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage (see section 2.6.1 *Undesirable Effects, Clinical Trials, Haemorrhage*). Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomized clinical studies (see section 2.6.1 *Undesirable Effects, Clinical Trials, Haemorrhage*). Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 2.6.2 Undesirable Effects, Post marketing)

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary Haemorrhage/Haemoptysis (see section 2.6 Undesirable Effects)

Patients with non-small cell lung cancer treated with bevacizumab may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see section 2.6.1 *Undesirable Effects, Clinical Trials, Haemorrhage*). Patients with recent pulmonary haemorrhage/haemoptysis (> 1/2 teaspoon red blood) should not be treated with bevacizumab.

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Preexisting hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Monitoring of blood pressure is recommended during bevacizumab therapy (see section 2.6.1 *Undesirable Effects, Clinical Trials, Hypertension*).

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy (see sections 2.6.1 *Undesirable Effects, Clinical Trials* and 2.6.2 *Undesirable Effects, Post marketing*).

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known (see sections 2.6.1 *Undesirable Effects, Clinical Trials, Posterior Reversible Encephalopathy Syndrome* and 2.6.2 *Undesirable Effects, Post marketing*).

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating such patients with bevacizumab.

Venous Thromboembolism (see section 2.6 Undesirable Effects)

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of venous thromboembolic events (see section 2.6.1 *Undesirable Effects, Clinical Trials, Venous Thromboembolism*).

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events $\leq$ Grade 3 need to be closely monitored.

Congestive Heart Failure (see section 2.6 Undesirable Effects)

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Bevacizumab.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. In both AVF3694g and AVF3693g, CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patient receiving chemotherapy alone. This is consistent with result in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (see section 2.6.1 *Undesirable Effects, Clinical Trials, Congestive Heart Failure*).

Neutropenia

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Bevacizumab in comparison to chemotherapy alone.

Wound Healing

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported.

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery (see section 2.6.1 *Undesirable Effects, Clinical Trials*).

Necrotising fasciitis including fatal cases, has rarely been reported in patients treated with Bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see section 2.6.2 *Undesirable Effects, Post marketing*).

Proteinuria (see section 2.6 Undesirable Effects)

In clinical trials, the incidence of proteinuria was higher in patients receiving Bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Bevacizumab. In the event of nephrotic syndrome, Bevacizumab treatment should be permanently discontinued.

Hypersensitivity Reactions, Anaphylactic Reactions (including Anaphylactic Shock), Infusion-Related Reactions (see section 2.6 Undesirable Effects, Post marketing)

Patients may be at risk of developing hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), and infusion-related reactions. Close observation of the patient during and following the administration of bevacizumab is recommended. If an anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered.

If an infusion-related reaction occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue Bevacizumab for severe (Grade ≥ 3) infusion related-reaction. A systematic premedication is not warranted.

Ovarian Failure/Fertility (see section 2.5.1 Use in Special Populations, Females and Males of Reproductive Potential and 2.6.1 Undesirable Effects, Clinical Trials)

Bevacizumab may impair female fertility. Therefore, fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with Bevacizumab.

2.4.2 Drug Abuse and Dependence

No information available.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machine have been performed. However, there is no evidence that bevacizumab treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

2.5 USE IN SPECIAL POPULATIONS**2.5.1 Females and Males of Reproductive Potential****Fertility**

Bevacizumab may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with Bevacizumab. (see section 2.4.1 *Warnings and Precautions, General and section 2.6.1 Undesirable Effects, Clinical Trials*)

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 3.3.3 *Impairment of Fertility*). A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

Contraception

In women with childbearing potential, appropriate contraceptive measures should be used during Bevacizumab therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of Bevacizumab.

2.5.2 Pregnancy

Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy.

There are no adequate and well-controlled studies in pregnant women (see section 3.3.4 *Reproductive Toxicity*). IgGs are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the foetus. In the post marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 2.6.2 *Undesirable Effects, Post marketing*).

Therefore, bevacizumab should not be used during pregnancy.

Labour and Delivery

No information available.

2.5.3 Lactation

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development, women should be advised to discontinue nursing during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.

2.5.4 Pediatric Use

Bevacizumab is not approved for use in patients under the age of 18 years. The safety and efficacy of bevacizumab in this population have not been established.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab (2.6.2 *Post marketing, section 3.3.5 Nonclinical Safety, Other (Physical Development)*).

2.5.5 Geriatric Use

Refer to section 2.4.1 *Warnings and Precautions* under the sub-heading *Arterial Thromboembolism*.

2.5.6 Renal Impairment

The safety and efficacy of Bevacizumab have not been studied in patients with renal impairment.

2.5.7 Hepatic Impairment

The safety and efficacy of Bevacizumab have not been studied in patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Summary of safety profile

Clinical trials have been conducted in patients with various malignancies treated with Bevacizumab, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5500 patients is presented in this section. For post marketing experience see section 2.6.2 *Post marketing*. See section 3.1.2 *Clinical/Efficacy Studies* for details of major studies, including study design and major efficacy results.

The most serious adverse drug reactions were

- Gastrointestinal Perforations (see section 2.4.1 *Warnings and Precautions, General*)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see section 2.4.1 *Warnings and Precautions, General*)
- Arterial Thromboembolism (see section 2.4.1 *Warnings and Precautions, General*)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose-dependent.

Bevabell has been evaluated in the clinical studies of Phase I and Phase III. The overall safety profile observed in these studies was consistent with that of the reference bevacizumab product.

In the Phase I study conducted in 99 healthy male subjects, the most frequently report treatment emergent adverse event (TEAE) was elevated serum triglycerides, occurring in 10.2% of subjects in the Bevabell group and 8.0% in the Avastin group.

In the Phase III study involving 548 patients with advance or current non-squamous non-small cell lung cancer, the most commonly reported TEAEs ($\geq 20\%$) included decreased white blood cell count, neutrophil count, platelet count, anaemia, hyperlipidaemia (including hypertriglyceridemia and hypercholesterolemia), alopecia, nausea, proteinuria, hypoesthesia, and asthenia. The most commonly reported treatment-related adverse events (TRAEs) ($\geq 20\%$) were decreased white blood cell count, neutrophil count, platelet count, anaemia, and proteinuria.

Tabulated summary of adverse drug reactions from clinical trials

The most frequently observed adverse drug reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhea and abdominal pain.

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC [Common toxicity criteria] grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC grade 1-5 reactions), in at least one of the major clinical trials. The adverse drug reactions listed in this table fall into the following categories: (Very common ($\geq 10\%$) and Common ($\geq 1\% - < 10\%$)). Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy, however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel.

Table 1 Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions ($\geq 2\%$ difference between the study arms in at least one clinical trial)		All Grade Reactions ($\geq 10\%$ difference between the study arms in at least one clinical trial)
	Very common	Common	Very common
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anemia	
Immune system disorder		Hypersensitivity, anaphylactic, infusion-related reactions	
Metabolism and nutritions disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased

Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Hemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnea Hypoxia Epistaxis	Dyspnea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhea Nausea Vomiting	Intestinal perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder Stomatitis	Constipation Stomatitis Rectal hemorrhage Diarrhea
Endocrine disorders			Ovarian failure*
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia	Arthralgia
Renal and urinary disorders		Proteinuria Urinary tract infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation

* Based on a substudy from AVF3077s (NSABP C-08) with 295 patients

Description of selected adverse drug reactions from clinical trials:

The following adverse drug reactions, reported using NCI-CTC for assessment of toxicity, have been observed in patients treated with bevacizumab.

Gastrointestinal Perforation and Fistula (see section 2.4.1 Warnings and Precautions, General)

Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2% in patients with metastatic renal cell cancer, or ovarian cancer and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established.

Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all bevacizumab treated patients.

In bevacizumab clinical trials, gastrointestinal fistula (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI- vaginal fistula was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistula may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistula (see section 2.4.1 Warnings and Precautions, General)

Bevacizumab use has been associated with serious cases of fistula including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG- 240), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistula.

Uncommon ($\geq 0.1\%$ to $< 1\%$) reports of other types of fistula that involve areas of the body other than the gastrointestinal tract (e.g., bronchopleural, urogenital and biliary fistula) were observed across various indications. Fistula have also been reported in post marketing experience.

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 0.5% in bevacizumab-treated patients, compared to 0 to 2.9% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

- ***Tumour-associated haemorrhage*** was observed in phase I and phase II studies. In patients with non-small cell lung cancer receiving bevacizumab, serious haemorrhage was observed in 9% (6% fatal) of treated patients.

Major or massive pulmonary haemorrhage/hemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with $< 1\%$ with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome (see section 2.4.1 *Warnings and Precautions, General*).

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhages were also seen rarely in other tumour types and locations and included cases of central nervous system (CNS) bleeding in patients with hepatoma with CNS metastases (see section 2.3 *Contraindications*) and continuous oozing of blood from a thigh sarcoma with necrosis.

The incidence of CNS bleeding in patients untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomized clinical studies. In an exploratory retrospective analysis of data from 13 completed randomized trials in patients with various tumour types, 3 patients out of 91

(3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab.

Across all bevacizumab clinical trials, **mucocutaneous haemorrhage** were seen in up to 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Hypertension (see section 2.4.1 Warnings and Precautions, General)

In clinical trials, the overall incidence of hypertension (all grades) of up to 42.1% in the bevacizumab containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab compared to up to 0.2% patients treated with the same chemotherapy alone.

Hypertension was generally adequately controlled with oral-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation (0.7% of bevacizumab-treated patients) or hospitalisation, and resulted in hypertensive encephalopathy in one case (0.1%).

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see section 2.4.1 *Warnings and Precautions, General*). The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 2.4.1 Warnings and Precautions, General)

Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Thromboembolism

- Arterial thromboembolism

An increased incidence of arterial thromboembolic events was observed in patients treated with bevacizumab across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 3.8% in the bevacizumab containing arms compared up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.7% of bevacizumab treated patients versus up to 0.5% of patients in the control group; myocardial infarction was reported in up to 1.4% bevacizumab treated versus up to 0.7% of patients in control groups.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group.

- Venous thromboembolism (see section 2.4.1 Warnings and Precautions, General)

In clinical trials of metastatic carcinoma of the colon or rectum, venous thromboembolic events including deep venous thrombosis, pulmonary embolism and thrombophlebitis occurred in 9.0% - 16.6% of bevacizumab-treated patients compared to that of 13.5% - 15.2% in the controls. It could not be determined if these events were due to the patients' underlying cancer, their cytotoxic chemotherapy, or other risk factors.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

Congestive Heart Failure

In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In five phase III studies (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer CHF Grade 3 or higher was reported in up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all grade CHF were similar between the anthracycline + bevacizumab (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA II–IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF (see section 2.4.1 *Warnings and Precautions, General*).

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m². This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/ vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm.

Wound Healing (see section 2.4.1 Warnings and Precautions, General)

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting bevacizumab treatment were excluded from participation in phase III trials. Across mCRC clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed, if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

Cases of serious wound healing complications have been reported during bevacizumab use, some of which had a fatal outcome (see section 2.4.1 *Warnings and Precautions, General*).

In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving bevacizumab compared with up to 0.9% patients in the control arms.

Proteinuria (see section 2.4.1 Warnings and Precautions, General)

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to < 3.1% of treated patients; however, in up to 7% of patients treated for advanced and/or metastatic renal cell carcinoma. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy.

In clinical trials of metastatic carcinoma of the colon or rectum, proteinuria was reported as an adverse event in 21.7% - 38.0% of bevacizumab-treated patients.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of ≥ 2 g/24 hours led to the holding of bevacizumab until recovery to < 2 g/24 hours.

Hypersensitivity Reactions, Anaphylactic Reactions (including Anaphylactic Shock), Infusion-Related Reactions (see sections 2.4.1 Warnings and Precautions, General and 2.6.2 Undesirable Effects, Post marketing)

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab-treated patients).

Ovarian Failure/Fertility (see sections 2.4.1 Warnings and Precautions, General and 2.5.1 Use in Special Populations, Females and Males of Reproductive Potential)

The incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Elderly Patients

In randomized clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks (TIAs) and myocardial infarctions compared to those aged ≤ 65 years when treated with bevacizumab (see sections 2.4.1 Warnings and Precautions, General and 2.6.1 Undesirable Effects, Clinical Trials, Thromboembolism). Other reaction with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia, and thrombocytopenia; and all Grade neutropenia, diarrhea, nausea, headache and fatigue.

From a clinical trial in patients with metastatic colorectal cancer (study AVF2107), no increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure and haemorrhage, was observed in elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

In the phase III study in metastatic carcinoma of colon or rectum trial (AVF2107g), 114 out of the 392 patients who received bevacizumab were older than 65 years. Only Grade 3/4 leukopenia occurred at an incidence of $\geq 5\%$ in the elderly patients (> 65 years) compared to those patients aged ≤ 65 years.

In the phase II study in metastatic carcinoma of colon or rectum trial (AVF2192g), the majority of the bevacizumab-treated patients was older than 65 years (83%). The overall safety profile of bevacizumab from this study was comparable to the overall safety profile observed in Study AVF2107g.

Laboratory Abnormalities

Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with bevacizumab treatment.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased ($\geq 2\%$) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased PT (prothrombin time), normalised ratio.

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting of suspicious adverse reactions after authorization of a medicinal product is important. This allows continuous monitoring of the benefit/risk balance of the drug. Health professionals are asked to report any suspected side effects to:

Pharmacovigilance - PT CKD OTTO Pharmaceuticals

Email: cs@ckd-otto.com

Tel: 0811-971-918

Or

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: <https://e-meso.pom.go.id/ADR>

2.6.2 Post Marketing

The following adverse drug reactions have been identified from postmarketing experience with Bevacizumab (Table 2) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$).

Table 2 Adverse Drug Reactions From Post Marketing Experience

Adverse reactions	Frequency Category
<i>Infections and Infestations</i>	
Necrotising fasciitis ^{1,2}	Rare
<i>Nervous system disorders</i>	
Hypertensive encephalopathy ^{2,3}	Very rare
Posterior Reversible Encephalopathy Syndrome (PRES) ²	Rare
<i>Vascular Disorders</i>	
Renal Thrombotic Microangiopathy, clinically manifested as proteinuria ^{2,3}	Unknown
<i>Respiratory, thoracic and mediastinal disorders</i>	
Nasal septum perforation	Unknown
Pulmonary hypertension	Unknown
Dysphonia	Common
<i>Gastrointestinal disorders</i>	
Gastrointestinal ulcer	Unknown
<i>Hepatobiliary disorders</i>	
Gallbladder perforation	Unknown
<i>Musculoskeletal and Connective Tissue disorders</i>	
Osteonecrosis of the Jaw (ONJ) ⁴	Unknown
Osteonecrosis at sites other than the jaw ^{5,6}	Unknown
<i>Congenital, familial and genetic disorders</i>	
Fetal abnormalities ⁷	Unknown

1. Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation

2. See section 2.4.1 Warnings and Precautions, General

3. See section 2.6.1 Undesirable Effects, Clinical Trials

4. Cases of ONJ-observed in Bevacizumab-treated patients mainly in association with prior or concomitant use of bisphosphonates.

5. Cases observed in Bevacizumab-treated pediatric patients. See section 2.5.4 Use in special populations, Pediatric use

6. Osteonecrosis observed in pediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.

7. Cases have been observed in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics. See section 2.5.2 Use in Special Populations, Pregnancy.

Description of selected adverse drug reactions from postmarketing experience

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis (frequency not known; some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular hemorrhage such as vitreous hemorrhage or retinal hemorrhage (frequency not known); Conjunctival hemorrhage (frequency not known).

2.7 OVERDOSE

The highest dose tested in humans (20 mg/kg of body weight every 2 weeks, intravenous) was associated with severe migraine in several patients.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant interaction of coadministered chemotherapy on Bevacizumab pharmacokinetics was observed based on the results of a population PK analyses. There was neither statistical significance nor clinically relevant differences in Bevacizumab clearance in patients receiving Bevacizumab monotherapy compared to patients receiving Bevacizumab in combination with interferon alfa 2a, or chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin, or gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of Bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and Bevacizumab has not been established.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese Hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at ≤ 0.35 ppm. Bevacizumab consist of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumour, thereby inhibiting tumour growth.

Pharmacodynamic effects

Administration of bevacizumab or its parenteral murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

3.1.2 Clinical/Efficacy Studies

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of bevacizumab (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomized, active-

controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Bevacizumab was combined with two chemotherapy regimens:

- **AVF2107g:** A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for total of 4 weeks of each 6 week-cycle.
- **AVF0780g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- **AVF2192g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Bevacizumab in Combination with IFL Chemotherapy for First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF2107g):

This was a phase III randomized, double-blind, active-controlled clinical trial evaluating Bevacizumab in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomized to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV + bevacizumab (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0.43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

Table 3 Treatment Regimens in Study AVF2107g

	Treatment	Starting Dose	Schedule
	Placebo	IV	Every 2 weeks
Arm 1	Irinotecan	125 mg/m ² IV	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m ² IV	
	Leucovorin	20 mg/m ² IV	
	Placebo	IV	Every 2 weeks
Arm 2	Irinotecan	125 mg/m ² IV	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m ² IV	
	Leucovorin	20 mg/m ² IV	
	Bevacizumab	5 mg/kg IV	Every 2 weeks
Arm 3	5-Fluorouracil	500 mg/m ² IV	Given once weekly for 6 weeks every 8 weeks
	Leucovorin	500 mg/m ² IV	
	Bevacizumab	5 mg/kg IV	Every 2 weeks
5-Fluorouracil : IV bolus injection immediately after leucovorin			
Folinic acid : IV bolus injection (over 1 – 2 minutes) immediately after each irinotecan dose			

The primary efficacy parameter of the trial was overall survival. The addition of bevacizumab to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 4). The clinical benefit of bevacizumab, as measured by survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease.

The efficacy results of bevacizumab in combination with IFL-chemotherapy are displayed in Table 4.

Table 4 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL + Placebo	Arm 2 IFL + Bevacizumab ^a
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio ^b	0.660 (p-value = 0.00004)	
Secondary endpoint:		
Progression-Free Survival		

Median (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.00001)	
Overall Response Rate	34.8%	44.8%
	(p-value = 0.0036)	

^a 5 mg/kg every 2 weeks

^b Relative to control arm

Among the 110 patients randomized to Arm 3 (5-FU/FA+Bevacizumab) prior to discontinuation of this arm, the median overall survival was 18.3 months, and the median progression free survival was 8.8 months.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum in Patients Who Were Not Optimal Candidates for First-Line Irinotecan Treatment (AVF2192g):

This was a phase II randomized, double-blind, active-controlled clinical trial evaluating the efficacy and safety of bevacizumab in combination with 5-FU/FA as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1 , baseline albumin < 3.5 g/dL) in order to be eligible for enrollment. One hundred and five patients were randomized to 5-FU/FA + placebo arm and 104 patients to 5-FU/FA + Bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The overall mean age was 71 years; 28.2% of patients had a ECOG performance status of 0, 65.1% had a value of 1, and 6.7% had a value of 2.

The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, compared to 5-FU/FA chemotherapy alone (see Table 5). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

Bevacizumab in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF0780g):

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomized to receive bolus 5-FU/FA or 5-FU/FA + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 5). These efficacy data are consistent with the results from study AVF2107g.

The efficacy data from studies AVF0780g and AVF2192g investigating bevacizumab in combination with 5-FU/FA-chemotherapy are summarized in Table 5.

Table 5 Efficacy Results from Study AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + Bevacizumab ^a	5-FU/FA + Bevacizumab ^b	5-FU/FA + placebo	5-FU/FA + Bevacizumab
Number of Patients	36	35	33	105	104
1. Overall Survival					
Median (months)	13.6	17.7	15.2	12.9	16.6
95% Confidence Interval				10.35 - 16.95	13.63 – 19.32
Hazard ratio ^c	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
2. Progression-Free Survival					

Median (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
3. Overall Response Rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% confidence interval	7.0 - 33.5	24.4 - 57.8	11.7 - 42.6	9.2 - 23.9	18.1 - 35.6
p-value	-	0.029	0.43		0.055
Duration of Response					
Median (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5 - NR	6.1 - NR	3.8 – 7.8	5.59 - 9.17	5.88 - 13.01

^a 5 mg/kg every 2 weeks

^b 10 mg/kg every 2 weeks

^c Relative to control arm

NR = Not reached

Locally recurrent or metastatic Breast Cancer (mBC)

ECOG E2100

E2100 was an open-label, randomized, active controlled, multicentre clinical trial evaluating bevacizumab in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Patients were randomized to paclitaxel alone (90 mg/m² IV over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued chemotherapy prematurely, treatment with bevacizumab as a single agent was continued until disease progression. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 6.

Table 6 Study E2100 Efficacy Results: Eligible Patients

Table 3. Progression-free survival (months) in the intent-to-treat population

Progression-free survival				
	Investigator Assessment*		IRF Assessment	
	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	<0.0001		<0.0001	
Response rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n=273)	Paclitaxel/Bevacizumab (n=252)	Paclitaxel (n=243)	Paclitaxel/Bevacizumab (n=229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	<0.0001		<0.0001	

* primary analysis

Overall survival		
	Paclitaxel (n=354)	Paclitaxel/Bevacizumab (n=368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722 ; 1.046)	
p-value	0.1374	

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of bevacizumab in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

E4599

E4599 was an open-label, randomized, active-controlled, multicentre clinical trial evaluating bevacizumab as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.

During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of bevacizumab and 21.1% (89/422) of patients received 13 or more administrations of bevacizumab.

The primary endpoint was duration of survival. Results are presented in Table 7.

Table 7 Efficacy results for study E4599

	Arm 1 Carboplatin/Paclitaxel	Arm 2 Carboplatin/Paclitaxel + Bevacizumab 15 mg/kg q 3 weeks
Number of Patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio		0.80 (p=0.003) 95% CI (0.69, 0.93)
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65 (p<0.0001) 95% CI (0.56, 0.76)
Overall Response Rate		
Rate (percent)	12.9	29.0 (p<0.0001)

China NSCLC Study-BEYOND

YO25404

Study YO25404 was a randomized, double-blind, placebo-controlled, multicenter Phase III study of bevacizumab used in addition to carboplatin and paclitaxel (CP) chemotherapy in Chinese patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC who had not received prior chemotherapy for advanced disease. The primary endpoint was progression-free survival, secondary endpoints for the study included overall survival and objective response.

Patients were randomized to CP (carboplatin AUC = 6.0 and paclitaxel 175 mg/m², both by IV infusion) on day 1 of every 3-week cycle for up to 6 cycles or CP in combination with bevacizumab at a dose of

15 mg/kg IV infusion on day 1 of every 3-week cycle. After completion of six cycles of CP chemotherapy or upon premature discontinuation of chemotherapy, patients were to continue to receive bevacizumab or placebo as a single agent every 3 weeks until disease progression or unacceptable toxicity.

Study results show that 78% (107/138) of patients in the bevacizumab-containing treatment arm went on to receive single agent bevacizumab at cycle 7, and 57% (78/138) of patients in the placebo-containing arm went on to receive single agent placebo at cycle 7. The efficacy results are presented in Table 8.

Table 8 Efficacy results for study YO25404

	Arm 1 Carboplatin/Paclitaxel + placebo	Arm 2 Carboplatin/Paclitaxel + Bevacizumab 15 mg/kg q 3 weeks
Number of Patients	138	138
Progression-Free Survival Median (months) Hazard ratio	6.5	9.2 0.4 (p<0.0001) 95% CI (0.29, 0.54)
Overall Response Rate* Rate (percent)	26.3	54.4 (p<0.0001)
Overall Survival Median (months) Hazard ratio	17.7	24.3 0.68 (p=0.0154) 95%CI (0.50, 0.93)

*Only patients with measurable disease at baseline were analyzed.

China NSCLC Study - TOT-CR-TAB008-III-01

Study TOT-CR-TAB008-III-01 was Phase III randomized, double-blind, positive parallel controlled, nationwide, multi-centered, and equivalent trial evaluating the efficacy and safety of Bevabell in combination with paclitaxel and carboplatin versus reference bevacizumab in combination with paclitaxel and carboplatin as first-line treatment in patients with unresectable, advanced, or recurrent non-squamous non-small cell lung cancer (NSCLC) who had not received prior chemotherapy for advanced disease.

Eligible subjects were randomly assigned to two groups via an Interactive Web Response System (IWRS) in a ratio of 1:1: Patients from the experimental arm received Bevabell in combination with PC regimen (paclitaxel and carboplatin) chemotherapy and those from the control arm received Bevacizumab in combination with PC regimen (paclitaxel and carboplatin) chemotherapy, and pre-specified randomization stratification factors were ECOG PS score (0 or 1), clinical stages (III or IV), and presence or absence of brain metastasis (yes or no).

The primary endpoint was Objective Response Rate (ORR) after 6 cycles of treatment. Secondary endpoints included Disease Control Rate (DCR), ORR after 2 cycles, Duration of Response (DOR), Progression-Free Survival (PFS), 1-year Overall Survival Rate (OSR), and Overall Survival (OS).

Efficacy Results for TOT-CR-TAB008-III-01

The study enrolled 548 subjects: 277 in the Bevabell arm and 271 in the Bevacizumab comparator (Avastin) arm

Table 9 Efficacy Results for TOT-CR-TAB008-III-01

Efficacy Parameter	Bevabell Arm	Bevacizumab comparator Arm	Result
ORR (FAS)	55.96%	55.72%	ORR ratio: 1.00 (90% CI: 0.89, 1.14)
ORR (PPS)	60.55%	58.30%	ORR ratio: 1.04 (90% CI: 0.92, 1.17)
DCR (FAS)	95.70%	95.37%	Ratio: 1.00 (90% CI: 0.97, 1.04), p = 0.8536
ORR after 2 Cycles (FAS)	50.00%	46.72%	Ratio: 1.07 (90% CI: 0.92, 1.24)
Median DoR (FAS)	245 days	219 days	p = 0.3526

Median PFS (FAS)	273 days	239 days	HR = 0.99 (95% CI: 0.80, 1.22), p = 0.9457
1-Year OSR (FAS)	66.21%	68.00%	p = 0.6793
Median OS (FAS)	611 days	581 days	HR = 1.06 (95% CI: 0.80, 1.40), p = 0.6549

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer Front-line Ovarian Cancer

The safety and efficacy of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that compared the effect of the addition of Bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218

The GOG-0218 study was a Phase III multicenter, randomized, double-blind, placebo controlled, three arm study evaluating the effect of adding Bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked stage III or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.

A total of 1873 patients were randomized in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of bevacizumab (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles (Bevacizumab commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of Bevacizumab (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles (Bevacizumab commenced at cycle 2 of chemotherapy) followed by continued use of bevacizumab (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression-Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 10.

Table 10 Efficacy results from study GOG-0218

Progression-free survival						
	Investigator Assessment ¹			IRC Assessment		
	CPP (n= 625)	CPB15 (n= 1248) ²	CPB15+ (n=1248) ²	CPP (n= 625)	CPB15 (n= 1248) ²	CPB15+ (n=1248) ²
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI) ³		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p –value ⁴		0.0204 ⁵	< 0.0001 ⁵		0.2663	< 0.0001
Objective response rate⁶						
	Investigator Assessment			IRC Assessment		
	CPP (n= 396)	CPB15 (n= 393)	CPB15+ (n= 403)	CPP (n= 474)	CPB15 (n= 460)	CPB15+ (n= 499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p-value ⁴		0.2341	0.2041		0.0106	0.0012
Overall survival⁷						
	CPP (n= 625)		CPB15 (n= 625) ²	CPB15+ (n= 623) ²		
Median OS (months)	40.6		38.8	43.8		
Hazard ratio (95% CI) ³			1.065 (0.908,1.249)	0.879 (0.745, 1.038)		
p-value ⁴			0.2197	0.0641		

¹ Primary PFS analysis

² Events prior to Cycle 7 from the CPB15 and CPB15+ arms were pooled for the analyses

³ Relative to the control arm; stratified hazard ratio

⁴ One-sided log-rank p-value

⁵ Subject to a p-value boundary of 0.0116

⁶ Patients with measurable disease at baseline

⁷ Final overall survival analysis

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone, had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received front-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO stage I or IIA (Grade 3 or clear cell histology only), or FIGO stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.

A total of 1528 patients were randomized in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles plus bevacizumab (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression-Free Survival (PFS) as assessed by the investigator.

The results of this study are summarized in Table 11.

Table 11 Efficacy results from study BO17707 (ICON7)

Progression-free survival		
	CP (n= 764)	CPB7.5+ (n=764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective response rate ¹		
	CP (n=277)	CPB7.5+ (n=272)
Response rate	41.9%	61.8%
	(p-value < 0.0001)	
Overall survival ²		
	CP (n= 764)	CPB7.5+ (n=764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

¹ in patients with measurable disease at baseline

² Final OS analysis when 46.7% of patients died

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS.

Recurrent Ovarian Cancer

GOG-0213

GOG-0213 was a phase III randomized controlled trial studying the safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior antiangiogenic therapy. The study evaluated the effect of adding bevacizumab to carboplatin+paclitaxel and continuing bevacizumab as a single agent compared to carboplatin+paclitaxel alone.

A total of 673 patients were randomized in equal proportions to the following 2 treatment arms.

- CP arm: Carboplatin (AUC5) and paclitaxel (175 mg/m² IV over 3 hours) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC5) and paclitaxel (175 mg/m² IV over 3 hours) and concurrent bevacizumab (15 mg/kg) every 3 weeks for 6 and up to 8 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also examined. Results are presented in Table 12.

Table 12 Efficacy results from study GOG-0213

Primary Endpoint		
Overall Survival (OS)		
	CP (n=336)	CPB (n=337)
Median OS (months)	37.3	42.6
Hazard ratio (95% CI)	0.823 (CI: 0.680, 0.996)	
p-value	0.0447	
Secondary Endpoints		
Progression-free survival		
	CP (n=336)	CPB (n=337)
Median PFS (months)	10.2	13.8
Hazard ratio [95% CI]	0.613 (CI: 0.521, 0.721)	
p-value	<0.0001	
Objective response rate*		
	CP* (n=286)	CPB* (n=274)
No. (%) of pts with objective response (CR, PR)	159 (55.6%)	213 (77.7%)
p-value	<0.0001	

*Intent-to-treat population with measurable disease at baseline

Treatment with bevacizumab at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles then followed by bevacizumab as a single agent resulted in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

AVF4095g

The safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment, was studied in a phase III randomized, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding bevacizumab to carboplatin and gemcitabine chemotherapy and continuing bevacizumab as a single agent to progression to carboplatin and gemcitabine alone.

A total of 484 patients with measurable disease were randomized in equal portions to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m² on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m² on Days 1 and 8) and concurrent Bevacizumab (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by Bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 13.

Table 13 Efficacy results from study AVF4095g

Progression-free survival				
	Investigator Assessment*		IRC Assessment	
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p –value	<0.0001		<0.0001	
Objective response rate				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
% pts with objective response	57.4%	78.5%	53.7%	74.8%
p –value	<0.0001		<0.0001	
Overall survival**				
	Placebo + C/G (n = 242)		Bevacizumab + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard ratio (95% CI)	0.952 [0.771; 1.176]		0.952 [0.771; 1.176]	
p-value	0.6479		0.6479	

* Primary analysis

** Final overall survival analysis performed when approximately 73% of the patients had died

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomized, two-arm Phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (paclitaxel, topotecan, or PLD) alone or in combination with bevacizumab:

- CT Arm (chemotherapy alone):
 - Paclitaxel 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
 - Topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m² dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
 - PLD 40 mg/m² as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After Cycle 1, the drug could be delivered as a 1-hour infusion.
- CT+BV Arm (chemotherapy plus bevacizumab):
 - The chosen chemotherapy was combined with bevacizumab 10 mg/kg IV every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m² on Days 1–5 on a every 3 weeks schedule).

Eligible patients had ovarian cancer that progressed within 6 months of previous platinum therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free-survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 14.

Table 14 Efficacy results from study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n=182)	CT+BV (n=179)

Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (n=144)	CT+BV (N=142)
% pts with objective response	18 (12.5%)	40 (28.2%)
p –value	0.0007	
Overall Survival (final analysis)**		
	CT (n=182)	CT+BV (n=179)
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 (0.678, 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses

*Randomized patients with measurable disease at baseline

** At the time of the final OS analysis (25 January 2013) 266 patients (73.7%) had died across the two treatment arms

Cervical Cancer

GOG-0240

The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomized, four arms, multi-centre phase III trial.

A total of 452 patients were randomized to receive either:

- Paclitaxel 135 mg/m² IV over 24 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 1 (q3w)
- Paclitaxel 135 mg/m² IV over 24 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 1 and bevacizumab 15 mg/kg IV on Day 1 (q3w)
- Paclitaxel 175 mg/m² over 3 hours on Day 1 and topotecan 0.75 mg/m² over 30 minutes on days 1-3 (q3w)
- Paclitaxel 175 mg/m² over 3 hours on Day 1 and topotecan 0.75 mg/m² over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg IV on Day 1 (q3w)

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 15.

Table 15 Overall efficacy by bevacizumab treatment (ITT population) from study GOG-0240

	Chemotherapy (n=225)	Chemotherapy + BV (n=227)
Primary Endpoint		
Overall Survival		
Median (months) ¹	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value ⁵ = 0.0132)	
Secondary Endpoints		
Progression-Free survival		

Median PFS (months) ¹	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54;0.81] (p-value ⁵ = <0.0001)	
Best Overall Response		
Response rate ²	76 (33.8%)	103 (45.4%)
95% CI for Response Rates ³	[27.6; 40.4]	[38.8; 52.1]
Difference in Response Rates	11.60	
95% CI for Difference in Response Rates ⁴	[2.4; 20.8]	
p-Value (Chi-squared Test)	0.0117	

¹ Kaplan-Meier estimates

² Patients with best overall response of confirmed CR or PR

³ 95% CI for one sample binomial using Pearson-Clopper method

⁴ Approximate 95% CI for difference of two rates using Hauck-Anderson method

⁵ log-rank test (stratified)

3.1.3 Immunogenicity

No robust assessment of anti-drug antibodies has been done in Bevacizumab clinical trials.

However, in the immunogenicity results of the phase I study of Bevabell titled "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", as for the pre dose results, all subjects were tested as ADA negative with the original analytical method; 1 (2.0%) subject in the Bevabell group and 2 (4.0%) subjects in the Avastin group were ADA positive when the alternative analytical method was adopted as a retrospective analysis, all of whom were ADA negative in all subsequent post dose test. As for post dose results, 1 (2.0%) subject in the Bevabell group and 1 (2.0%) subject in the Avastin group reported positive ADA result, at Day 15 and Day 85, respectively. These 2 subjects showed negative NAb results. Both subjects have recovered to ADA negative. Neutralizing antibody was not assessed for other subjects.

In the immunogenicity results of the phase III study of Bevabell titled "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", descriptive statistics were used to summarize immunogenicity variables, including positive rate of anti-drug antibody (ADA) and positive rate of neutralizing antibody (NAb).

Throughout the trial, a total of 8 subjects developed anti-drug antibodies (ADA), including 3 subjects (1.08%) in the experimental arm and 5 subjects (1.85%) in the control arm; at the end of the study, 7 of these 8 subjects tested ADA positive, with sustainability, including 3 subjects (100.0%) in the experimental arm and 4 subjects (80.0%) in the control arm. Only one subject (control group) developed a neutralizing antibody NAb, and this subject was tested negative for NAb at the end of the study. One subject (16032) who developed ADA died in the experimental arm and the cause of death was disease progression. Three of the subjects who developed ADA had serious adverse events, all in the control arm: 34004 (myelosuppression, with outcome of being resolved without sequelae), 10007 (thrombocytopenia, with outcome of symptom ongoing), 45011 (pneumothorax grade 2, with outcome of being resolved without sequelae), with no apparent difference in safety from overall. Two of the subjects with ADA were subjected to PK analysis, both from the control arm (34004, 32003). After multiple intravenous infusions of 15 mg/kg Bevabell, in the PKs, the mean trough serum concentration ($\pm$ SD) in the control arm was 100.63 μ g/mL ($\pm$ 30.62), the mean serum concentration in Subject 34004 was 93.51 μ g/mL ($\pm$ 7.55), the mean serum concentration in Subject 32003 was 127.76 μ g/mL ($\pm$ 11.41), and the serum concentration was not significantly different from overall.

3.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterized by a low clearance, a limited volume of the central compartment (V_c), and a long elimination half-life. This

enables target therapeutic bevacizumab serum levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In a population pharmacokinetic meta-analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to race when body weight is taken into account, or in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 year with 5th and 95th percentiles of 37 and 76 year]).

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

In the pharmacokinetic results of the phase I study of Bevabell titled "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", the mean concentration curve of Bevabell and Avastin was similar. The LS geometric means for the 3 primary PK parameters of subjects in the experimental arm were fully contained within the bioequivalence margin of 80.00% to 125.00% (90% CI: 103.66% to 118.33% for C_{max}, 94.32% to 111.72% for AUC_{0-t}, and 94.69% to 112.23% for AUC_{0-∞}). Based on the results of non-parametric analysis, the t_{max} of Bevabell and Avastin were the same (the median difference was equal to 0). All other secondary PK parameters were similar between treatment groups

In the pharmacokinetic results of the phase III study of Bevabell titled "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", the mean of steady-state trough concentration of each subject, as well as the arithmetic mean, standard deviation, geometric mean and 90% confidence interval (CI) of geometric mean ratio of steady-state trough concentration of subjects in the experimental arm and the control arm were calculated, and the equivalent test on the steady-state trough concentration of TAB008 monoclonal antibody and bevacizumab was conducted.

3.2.1 Absorption

In the pharmacokinetic results of the non clinic study for Bevabell titled "Report on Pharmacokinetic Studies on TAB008 Monoclonal Antibody Injection in Rhesus Monkeys Following Intravenous Infusion", after intravenous infusion of Bevabell at different doses (1, 5, 25 mg/kg) to rhesus monkeys (*vd*), the pharmacokinetic characteristics of Bevabell were basically linear within the dose range studied. Repeated administration of Bevabell at a medium dose lead to drug accumulation, with an accumulation factor of 1.69 ± 0.31 . At the same dose (5 mg/kg), the pharmacokinetic parameters of Bevabell was comparable to that of Avastin. Compared with the reference drug, the relative bioavailability of Bevabell was 121.06%.

3.2.2 Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male subjects respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is coadministered with anti-neoplastic agents. After correcting for body weight, male subjects had a larger V_c (+ 20%) than females.

3.2.3 Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ¹²⁵I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor result in protection from cellular metabolism and the long terminal half-life.

3.2.4 Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk.

The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

3.2.5 Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Pediatric Population: The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between pediatric and adult patients when normalized by body weight. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

Renal impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.

3.3 Nonclinical safety

3.3.1 Carcinogenicity

Studies have not been performed to evaluate the carcinogenic potential of bevacizumab.

3.3.2 Genotoxicity

Studies have not been performed to evaluate the mutagenic potential of bevacizumab.

3.3.3 Impairment of Fertility

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on male reproductive organs was observed in repeat dose toxicity studies in cynomolgus monkeys.

Inhibition of ovarian function was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with bevacizumab for 13 or 26 weeks. The doses associated with this effect were ≥ 4 times the human therapeutic dose or ≥ 2 -fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of bevacizumab resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of bevacizumab is likely to result in an adverse effect on female fertility.

3.3.4 Reproductive Toxicity

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse fetal outcomes were observed at all tested doses of 10-100 mg/kg. Information on fetal malformations observed in the post marketing setting are provided in sections 2.5.2 *Use in Special Populations*, *Pregnancy* and 2.6.2 *Undesirable Effects, Post Marketing*.

3.3.5 Toxicology

Single-Dose Toxicity:

The objective of the study of Bevacizumab was to evaluate the acute toxicity of Bevacizumab after a single dose administration to ICR mice via intravenous injection using maximal dosage method, and provide animal data for clinical study. The mice were treated via single intravenous injection with a volume of 25 mL/kg. After dosing, the mice were observed for 4 consecutive hours on Day 1 and twice daily (am and pm)

for 14 consecutive days. After the 14 days observations, animals were euthanized and received a gross necropsy examination. Tissues with gross lesion were fixed and microscopic examination was performed. No apparent abnormal changes in clinical observations for 4 consecutive hours after dosing and during the 14 days observations. No apparent abnormal changes in body weight, or food consumption were noted in any animals when compared with the adjuvant control group. No apparent test article-related abnormal changes in gross necropsy and microscopic examination were noted in any animals. In this study, no apparent toxicity was observed in ICR mice after intravenous injection of Bevabell and the maximum tolerated dose (MTD) was greater than or equal to 625 mg/kg.

Moreover, the objectives of the study of Bevabell were to evaluate the acute toxicity of TAB008 monoclonal antibody injection after a single dose administration to cynomolgus monkeys via intravenous infusion, and provide animal experimental information for the repeated toxicity study and clinical usage.

Those cynomolgus monkeys were observed approximately 4 consecutive hours after dosing. All animals were euthanized and subjected to macroscopic examinations at the end of the observation period. Under the conditions of this study, no obvious changes were noted in all detected indexes in cynomolgus monkeys treated with a single dose of TAB008 monoclonal antibody injection at 100, 200, and 400 mg/kg via intravenous infusion, except for the temporarily elevated AST in all groups. On the basis of these results, the maximum tolerance dose (MTD) of TAB008 monoclonal antibody injection to cynomolgus monkeys is determined to be greater than or equal to 400 mg/kg

Repeat-Dose Toxicity, Antigenicity, Immunotoxicity, Local Tolerance:

After Cynomolgus monkeys were given repeated intravenous infusion of Bevabell at the doses of 2, 10, 50 mg/kg, twice weekly for 4 weeks, 9 times in total, femoral growth plate dysplasia related to the pharmacological action of test article were noted, but no other toxicities were observed. Therefore, the safe dose was 50 mg/kg, approximately 10 times the proposed human clinical dose (mg/kg). After Cynomolgus monkeys were given repeated intravenous infusion of Bevabell, anti-TAB008 antibodies occurred in the 2 and 10 mg/kg dose groups, but the antibody occurrence rate of the former was significantly higher. The antibody had no neutralizing effect on the activity of Bevabell. After Cynomolgus monkeys were given repeated intravenous infusion of 2-50 mg/kg Bevabell, the *in vivo* exposure level was proportionally increased with the dosages used, the degrees of accumulation in different dose groups were comparable, and the accumulation ratios were 2.41-2.91. There was no sexual difference in the TK properties. After Cynomolgus monkeys were given repeated intravenous infusion of 0.25-6.25 mg/ml Bevabell twice weekly, no test article-related irritant reaction was noted at the injection sites. The toxicities of Bevabell were basically consistent with those of the commercial drug Avastin.

3.3.6 Other

Physeal Development:

In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Wound Healing:

In rabbits, the effects of bevacizumab on circular wound healing were studied. Wound re-epithelialisation was delayed in rabbits following five doses of bevacizumab, ranging from 2-50 mg/kg, over a 2-week period. A trend toward a dose-dependent relationship was observed. The magnitude of effect on wound healing was similar to that observed with corticosteroid administration. Upon treatment cessation with either 2 or 10 mg/kg bevacizumab, the wounds closed completely. The lower dose of 2 mg/kg was approximately equivalent to the proposed clinical dose. A more sensitive linear wound healing model was also studied in rabbits. Three doses of bevacizumab ranging from 0.5-2 mg/kg dose-dependently and significantly decreased the tensile strength of the wounds, consistently with delayed wound healing. The low dose of 0.5 mg/kg was 5-fold below the proposed clinical dose. As effects on wound healing were observed in rabbits at doses below the proposed clinical dose, the capacity for bevacizumab to adversely impact wound healing in human should be considered.

In cynomolgus monkeys, the effects of bevacizumab on the healing of a linear incision were highly variable and no dose-response relationship was evident.

Renal Function:

In normal cynomolgus monkeys, bevacizumab had no measurable effect on renal function treated once or twice weekly for up to 26 weeks, and did not accumulate in the kidney of rabbits following two doses up to 100 mg/kg (approximately 80-folds the proposed clinical dose).

Investigative toxicity studies in rabbits, using models of renal dysfunction, showed that bevacizumab did not exacerbate renal glomerular injury induced by bovine serum albumin or renal tubular damage induced by cisplatin.

Albumin:

In male cynomolgus monkeys, Bevacizumab administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

At doses up to 50 mg/kg twice weekly in cynomolgus monkeys, bevacizumab showed no effects on blood pressure.

Haemostasis:

Nonclinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not find changes in haematology or coagulation parameters including platelet counts, prothrombin and activated partial thromboplastin time. A model of haemostasis in rabbits, used to investigate the effect of bevacizumab on thrombus formation, did not show alteration in the rate of clot formation or any other haematological parameters compared to treatment with bevacizumab vehicle.

Anaphylactic:

Under the current study conditions, active systemic anaphylaxis test of Bevacizumab (5, 25mg/kg for sensitization; 10, 50mg/kg for challenge) in Guinea Pigs was positive.

Tissue Cross-Reactivity:

Bevacizumab and positive control AVASTIN could specifically react with human colon carcinoma. Bevacizumab and AVASTIN could not react with normal SD rat tissues, normal cynomolgus monkey tissues, normal human tissues.

Hemolysis:

Bevacizumab had hemolysis effect but no aggregation effect at 16.5 mg/mL, and Bevacizumab had no hemolysis or aggregation effect at 1.4 mg/mL in hemolysis test using rabbit RBCs under the current study condition. The results were similar to the marketed comparator Avastin.

4. PHARMACEUTICAL PARTICULARS**4.1 STORAGE**

Bevacizumab should not be used after the expiry date (EXP) shown on the pack.
Store vials in a refrigerator at 2°C-8°C and protect from light.

DO NOT FREEZE. DO NOT SHAKE.

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions [(see “Incompatibilities” below)].

Do not administer as an intravenous push or bolus.

Bevacizumab should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare Bevacizumab. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL.

Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Bevacizumab is not formulated for intravitreal use.

Incompatibilities

No incompatibilities between Bevacizumab and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of Bevacizumab was observed when diluted with dextrose solutions (5%).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

4.3 PACKS

Box, 1 vial @ 4 mL

Reg.No.: DKI.....

Medicine: keep out of reach and sight of children
Obat: Jauhkan dari jangkauan anak-anak
On medical prescription only
Harus dengan resep dokter

Manufacturer by:

BioDlink Biopharm Co., Ltd.
Suzhou – Cina

Imported by:

PT CKD OTTO Pharmaceuticals
Bekasi – Indonesia