Leaflet kemasan: Informasi untuk pengguna

ATGAM® 50 mg/ml konsentrat untuk larutan infus
Imunoglobulin Anti-Timosit (Kuda)

Baca semua bagian leaflet ini dengan cermat sebelum mulai menggunakan obat ini karena berisi informasi penting bagi Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, sekalipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 9.

Isi leaflet ini:

1. Nama produk
ATGAM®

2. Keterangan produk
ATGAM® adalah larutan dengan pelarut air steril yang bening hingga sedikit keruh, tidak berwarna hingga berwarna merah muda terang atau cokelat muda. Sedikit endapan berupa butiran atau serpihan mungkin akan terbentuk selama penyimpanan.

Tersedia dalam kemasan dus berisi 5 ampul masing-masing berisi 5 ml konsentrat steril.

3. Apa kandungan obat ini?

Zat aktifnya adalah Imunoglobulin Anti-Timosit (Kuda). Setiap ampul konsentrat steril berisi 250 mg Imunoglobulin Anti-Timosit (Kuda).

Bahan-bahan yang lain adalah glisin, air untuk injeksi, natrium hidroksida (untuk penyesuaian pH), dan asam hidroklorida (untuk penyesuaian pH) (lihat bagian 8 “ATGAM® mengandung natrium”).

4. Kekuatan obat
50 mg/ml.

5. Apa kegunaan obat ini?
ATGAM® dibuat dengan menyuntikkan sel timus manusia kepada kuda. Obat ini mengandung imunoglobulin (antibodi) yang menempel pada dan memusnahkan sebagian sel-sel sistem imun dalam tubuh Anda. Penggunaannya ditujukan untuk mengobati kondisi yang disebut anemia aplastik. Anemia aplastik terjadi saat sistem imun tubuh menyerang sel-selnya sendiri dan sumsum tulang tidak memproduksi cukup sel darah merah, sel darah putih, dan trombosit. Jika digunakan bersama dengan obat-obatan lainnya, ATGAM® membantu sumsum tulang untuk memproduksi sel-sel darah ini kembali. Obat ini juga dapat membantu menghindari kebutuhan akan transfusi darah. Obat-obatan yang menekan sistem imun tidak membantu menyembuhkan anemia aplastik. Akan tetapi dapat meredakan gejalanya dan mengurangi komplikasi. Obat-obatan ini sering kali digunakan untuk orang yang tidak dapat menjalani transplantasi sel punca darah dan sumsum tulang atau yang sedang menunggu untuk menjalani prosedur transplantasi sumsum tulang. ATGAM® dapat digunakan pada anak-anak berusia dua tahun ke atas serta pada orang dewasa.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini? Apa yang harus dilakukan jika ada dosis yang terlewat?
ATGAM® diberikan melalui infus ke dalam pembuluh vena oleh dokter atau tenaga kesehatan profesional. Anda harus bertanya kepada dokter atau apoteker untuk memperoleh informasi tambahan.

Petunjuk terperinci mengenai persiapan dan pemberian infus ATGAM® tercantum di bagian akhir leaflet ini. Petunjuk tersebut ditujukan untuk tenaga kesehatan profesional.

Dosis yang dianjurkan didasarkan pada berat badan (bb).

Total dosis yang dianjurkan adalah 160 mg/kg berat badan dengan terapi imunosupresif tambahan.

Anda dapat menerima ATGAM® dengan dosis sebagai berikut:
- 16 mg/kg bb/hari dalam waktu 10 hari atau.
- 20 mg/kg bb/hari dalam waktu 8 hari atau.
- 40 mg/kg bb/hari dalam waktu 4 hari.

Sebelum ATGAM® diberikan, Anda mungkin akan menerima obat-obatan lain (seperti kortikosteroid dan antihistamin) untuk membantu mencegah kemungkinan efek samping terkait dengan pemberian infus tersebut. Anda mungkin juga akan menerima obat untuk meredakan demam.

Jika Anda lupa menggunakan ATGAM®

Karena ATGAM® akan diberikan oleh dokter atau perawat, maka sangat kecil kemungkinan Anda tidak menerima obat ini pada waktu yang tepat. Jika Anda merasa belum menerima ATGAM® pada waktu yang semestinya, segera beri tahu dokter atau perawat Anda.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

7. Kapan seharusnya Anda tidak menggunakan obat ini?
Jangan menggunakan ATGAM®

- Jika Anda alergi terhadap zat aktif (Imunoglobulin Anti-Timosit (Kuda)) atau terhadap bahan-bahan lain yang terkandung dalam obat ini (tercantum di bagian 3).
- Jika Anda alergi terhadap sediaan gamma globulin kuda lainnya.

8. Apa yang harus dipertimbangkan saat menggunakan obat ini?
Hanya dokter yang berpengalaman dalam terapi imunosupresif yang dapat mengobati Anda dengan ATGAM®. Fasilitas pengobatan harus memiliki staf terlatih yang dapat mengakses sumber daya penunjang medis. Selama menjalani pengobatan dengan ATGAM® pasien akan terus dipantau.

Berkonsultasilah dengan dokter atau perawat Anda sebelum menerima ATGAM®

- Jika Anda merasa bahwa Anda mengalami infeksi atau memiliki gejala yang mengarah pada infeksi seperti demam, berkeringat, menggigil, nyeri otot, batuk, sesak napas, kulit terasa hangat, memerah, atau nyeri, atau terdapat luka pada tubuh Anda, diare atau sakit perut (atau gejala lain yang tercantum di bagian 9).
- Jika Anda harus divaksinasi. Vaksin menjadi kurang efektif jika diberikan bersama ATGAM®. Dokter akan memutuskan waktu yang tepat bagi Anda untuk menerima vaksin.

Jika obat-obatan terbuat dari darah atau plasma, akan dilakukan langkah-langkah khusus untuk mencegah penularan infeksi kepada pasien. Di antaranya:

- Pemilihan donor darah dan plasma dengan saksama untuk memastikan tidak diikutkannya orang yang berisiko menularkan infeksi.
- Pengujian terhadap setiap darah yang didonorkan dan kumpulan plasma untuk mengetahui adanya tanda-tanda virus/infeksi.
- Memasukkan langkah-langkah pemrosesan darah atau plasma untuk menonaktifkan atau menghilangkan virus.

Meskipun langkah-langkah di atas telah dilakukan, tetapi pemberian obat-obatan yang terbuat dari darah atau plasma tidak dapat meniadakan sepenuhnya kemungkinan penularan infeksi. Kondisi ini juga berlaku untuk virus yang tidak diketahui atau baru muncul untuk jenis infeksi lainnya.

Berikan perhatian khusus selama pengobatan dengan ATGAM®

Segera beri tahu dokter Anda jika Anda mengalami efek samping ATGAM® mana pun yang bersifat serius dan mengancam nyawa berikut ini (gejala-gejala yang memerlukan kontak langsung dengan dokter Anda disebutkan kembali di bagian 9):

- setiap infeksi serius: gejala-gejalanya antara lain demam, berkeringat, menggigil, nyeri otot, batuk, sesak napas, kulit terasa hangat, memerah, atau nyeri, atau terdapat luka pada tubuh Anda, diare atau sakit perut;

- reaksi alergi: gejalanya dapat meliputi ruam yang merata, peningkatan denyut jantung, kesulitan bernapas, penurunan tekanan darah, dan tubuh terasa lemah;
- penyakit serum: reaksi alergi yang menyebabkan demam, pegal dan nyeri pada persendian, ruam kulit, dan pembengkakan kelenjar getah bening;
- lapisan kulit teratas dapat tertarik menjauh dari posisi normalnya pada bagian tubuh mana pun;
- demam, pembengkakan, menggigil, peningkatan denyut jantung, penurunan tekanan darah, dan kesulitan bernapas. Gejala-gejala ini dapat mengarah pada kondisi yang disebut sindrom pelepasan sitokin.

Pengujian tambahan

Dokter akan melakukan tes darah sebelum Anda mulai menerima ATGAM®, selama dan setelah pengobatan, untuk mengetahui apakah jumlah sel darah putih rendah, jumlah sel darah merah rendah, atau terjadi penurunan jumlah trombosit. Jika terjadi abnormalitas sel darah yang berat, pengobatan dengan ATGAM® dapat dihentikan.

Untuk mengidentifikasi apakah Anda berisiko lebih tinggi mengalami reaksi alergi yang berat, tes pada kulit mungkin dilakukan sebelum pengobatan dilakukan. Pengujian bertujuan untuk memeriksa adanya alergi terhadap bahan-bahan ATGAM®. Hasil tes akan membantu dokter untuk memutuskan apakah ATGAM® dapat diberikan atau tidak.

Hasil tes fungsi hati dan ginjal yang abnormal bisa saja terjadi selama pasien dengan anemia aplastik menjalani pengobatan dengan ATGAM®.

ATGAM® mengandung natrium

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per total dosis, sehingga pada dasarnya bisa dikatakan ‘bebas-natrium’. Akan tetapi, penyiapannya bisa saja menggunakan larutan yang mengandung natrium. Beri tahu dokter Anda jika Anda sedang menjalani diet rendah garam (natrium).

9. Apa saja potensi efek yang tidak diinginkan dari penggunaan obat ini?
Seperti obat-obatan lainnya, obat ini dapat menimbulkan efek samping, sekali pun tidak semua orang mengalaminya.

Segera beri tahu dokter Anda jika Anda mengalami efek samping ATGAM® mana pun yang bersifat serius dan mengancam nyawa berikut ini (gejala-gejala yang memerlukan kontak langsung dengan dokter juga disebutkan di bagian 8 di atas):

- infeksi serius (sangat umum): gejala-gejalanya antara lain demam, berkeringat, menggigil, nyeri otot, batuk, sesak napas, kulit terasa hangat, memerah, atau nyeri, atau terdapat luka pada tubuh Anda, diare atau sakit perut;
- reaksi alergi (tidak umum),: gejalanya dapat meliputi ruam yang merata, peningkatan denyut jantung, kesulitan bernapas, penurunan tekanan darah, dan tubuh terasa lemah;
- penyakit serum (sangat umum): reaksi alergi yang menyebabkan demam, pegal dan nyeri pada persendian, ruam kulit, dan pembengkakan kelenjar getah bening;
- lapisan kulit teratas tertarik menjauh dari posisi normalnya pada bagian tubuh mana pun (frekuensi tidak diketahui).

Efek samping lainnya

Sangat umum: dapat dialami lebih dari 1 di antara 10 orang
- jumlah sel darah putih rendah.
- ruam kulit, kulit memerah, gatal-gatal pada kulit, iritasi kulit.
- kaligata.
- nyeri, termasuk pada persendian, punggung, dada, otot, tangan dan kaki, bagian samping.
- demam, menggigil, sakit kepala.
- infeksi (bakteri dan virus).
- tekanan darah tinggi atau rendah.
- diare, nyeri abdomen, mual.
- pembengkakan pada lengan atau kaki.
- hasil tes fungsi hati abnormal.

Umum: dapat dialami hingga 1 di antara 10 orang
- penguraian sel darah merah.
- kelenjar getah bening membesar atau membengkak.
- pusing, pingsan, merasa tidak enak badan.
- Kejang.
- kesemutan atau mati rasa pada tangan atau kaki.
- denyut jantung cepat atau lambat.
- pembengkakan dan nyeri pada bagian tubuh yang disebabkan oleh bekuan darah lokal dalam pembuluh vena.
- sesak napas atau kesulitan bernapas, napas terhenti sementara, muntah.
- mimisan.
- batuk.
- cairan di dalam paru-paru.
- perdarahan lambung atau usus.
- luka di dalam mulut, pembengkakan mulut, nyeri mulut.
- peningkatan kadar gula darah.
- abnormalitas ginjal.

Tidak umum: dapat dialami hingga 1 di antara 100 orang
- agitasi.
- kemerahan, pembengkakan, nyeri pada lokasi infus.
- pembengkakan di sekitar mata.
- memar atau perdarahan lebih lama daripada biasanya jika Anda terluka – ini mungkin merupakan tanda-tanda rendahnya jumlah trombosit darah (trombositopenia).

Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia
- pembengkakan otak yang menyakitkan, pembengkakan pembuluh darah yang menyakitkan.
- kesulitan bergerak, otot kaku.
- kebingungan, tremor.
- gagal jantung.
- bekuan dalam pembuluh darah usus halus, lubang pada usus halus (perforasi).
- kejang tenggorokan, cegukan.
- keringat berlebihan, berkeringat pada malam hari.
- terbukanya luka kembali.

- kurangnya perkembangan sel.
- hilangnya kekuatan atau energi.
- cedera ginjal.

Melaporkan efek samping
Jika Anda mengalami efek samping apa pun yang disebutkan di atas, konsultasikan dengan dokter, apoteker, atau perawat Anda. Anda harus melakukan langkah yang sama untuk efek samping yang tidak dicantumkan dalam leaflet ini.

Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi lainnya tentang keamanan obat ini. Untuk melaporkan efek samping, hubungi www.pfizersafetyreporting.com atau email di IDN.AEReporting@pfizer.com.

10. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?
Beri tahu dokter jika Anda sedang meminum, baru-baru ini telah meminum, atau mungkin meminum obat-obatan lainnya.

Saat dosis kortikosteroid dan imunosupresan lainnya dikurangi, beberapa reaksi terhadap ATGAM® yang sebelumnya tersembunyi bisa saja muncul. Anda akan dipantau secara ketat selama pemberian infus ATGAM® untuk melihat kondisi tersebut.

11. Apakah obat ini aman untuk ibu hamil dan menyusui?
Kehamilan

Beri tahu dokter Anda jika Anda menduga diri Anda hamil.

Tidak diketahui apakah ATGAM® dapat memengaruhi janin selama kehamilan. Oleh karena itu lebih diutamakan untuk menghindari penggunaan ATGAM® selama kehamilan.

Jika Anda hamil saat menggunakan obat ini, segera beri tahu dokter Anda.

Perempuan usia produktif harus menggunakan metode pengendali kelahiran (kontrasepsi) yang efektif selama menggunakan ATGAM® dan hingga 10 minggu setelah dosis terakhir. Konsultasikan dengan dokter Anda mengenai metode pengendali kelahiran yang tepat untuk Anda.

Menyusui

Beri tahu dokter Anda jika Anda sedang menyusui atau berencana untuk menyusui.

Belum diketahui apakah ATGAM® dapat dikeluarkan bersama ASI. Risiko bagi anak yang meminum ASI belum dapat dikesampingkan.

Anda dan dokter Anda harus memutuskan apakah Anda tetap menyusui atau menjalani pengobatan dengan ATGAM®.

12. Apakah pasien diizinkan mengemudi dan mengoperasikan mesin saat menggunakan obat ini?
ATGAM® dapat memengaruhi kemampuan Anda untuk mengemudi dan mengoperasikan mesin. Diperlukan kehati-hatian saat mengemudi atau mengoperasikan mesin selama menggunakan obat ini.

13. Bagaimana cara menyimpan obat ini?

- Jauhkan dari jangkauan dan penglihatan anak-anak.
- Umur simpan: 24 bulan.
- Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada kemasan setelah tulisan 'EXP'. Tanggal kedaluwarsa mengacu pada tanggal terakhir pada bulan tersebut.
- Simpan ampul dalam lemari pendingin (2–8°C). Jangan dibekukan. Simpan ampul dalam karton pembungkusnya agar terhindar dari paparan cahaya.

14. Tanda-tanda dan gejala-gejala overdosis

Efek samping mana pun yang disebutkan di atas mungkin terjadi.

15. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?

Karena ATGAM® akan diberikan oleh dokter atau perawat, sangat kecil kemungkinan ATGAM® diberikan melebihi dosis yang dianjurkan. Jika Anda merasa ATGAM® diberikan kepada Anda melebihi dosis yang diresepkan, segera beri tahu dokter atau perawat Anda.

16. Berapa lama masa simpan obat sejak wadahnya pertama kali dibuka?

Larutan yang diencerkan dapat disimpan pada suhu ruang (20–25°C). Larutan harus digunakan dalam waktu 24 jam (termasuk waktu infus).

Dari sudut pandang mikrobiologi, kecuali jika metode pembukaan/pengenceran mampu meniadakan risiko kontaminasi mikrobial, ampul terbuka atau produk obat yang terdapat di dalam syringe harus segera digunakan. Jika tidak segera digunakan, waktu penyimpanan selama penggunaan dan kondisi sebelum penggunaan menjadi tanggung jawab pengguna dan pengenceran harus dilakukan dalam kondisi aseptik yang terkontrol dan telah divalidasi.

17. Petunjuk penggunaan

Petunjuk terperinci mengenai persiapan dan pemberian infus ATGAM® tercantum di bagian akhir leaflet ini. Petunjuk tersebut ditujukan untuk tenaga kesehatan profesional.

18. Nama produsen/pemegang hak pemasaran

Diproduksi oleh:
Pharmacia & Upjohn Company LLC
Kalamazoo, Michigan, USA

Diimpor oleh:
PT. Pfizer Indonesia
Jakarta, Indonesia

19. Tanggal revisi

10/2024

20. Peringatan khusus

HARUS DENGAN RESEP DOKTER

Informasi berikut ini ditujukan untuk tenaga kesehatan profesional saja:

Penyiapan larutan
Setelah diencerkan, untuk pemberian intravena saja.

ATGAM® (diencerkan atau tidak diencerkan) tidak boleh dikocok karena dapat menimbulkan busa berlebihan dan/atau denaturasi protein. ATGAM® harus diencerkan sebelum pemberian infus dengan cara membolak-balik wadah yang telah diberi pelarut steril sedemikian rupa sehingga ATGAM® yang diencerkan tidak bersinggungan dengan udara yang ada di dalam wadah tersebut.

Tambahkan total dosis harian ATGAM® ke dalam botol atau kantong yang dibalik yang berisi salah satu pelarut steril berikut ini:
- natrium klorida 0,9%,
- Larutan glukosa/larutan natrium klorida:
- 50 mg/ml (5%) glukosa dalam larutan natrium klorida 0,45% (4,5 mg/ml),
- 50 mg/ml (5%) glukosa dalam larutan natrium klorida 0,225% (2,25 mg/ml).

Karena adanya kemungkinan mengendapnya ATGAM®, maka tidak disarankan untuk mengencerkannya dengan larutan glukosa saja.

Larutan yang diencerkan harus diputar-putar atau diayun-ayun perlahan untuk memberikan efek pencampuran sempurna.

Konsentrasi yang dianjurkan untuk ATGAM® yang diencerkan adalah 1 mg/ml dalam larutan natrium klorida 0,9%. Konsentrasinya tidak boleh melebihi 4 mg/ml ATGAM®.

ATGAM® yang diencerkan harus dibiarkan hingga mencapai suhu ruang (20–25°C) sebelum infus diberikan. Volume infus yang dapat digunakan adalah antara 250 ml hingga 500 ml. ATGAM® harus diberikan ke dalam pembuluh vena pusat aliran tinggi melalui filter in-line (di dalam saluran infus) (0,2–1,0 mikron).

Filter in-line (tidak disediakan) harus digunakan saat memberikan infus ATGAM® untuk mencegah masuknya bahan yang tidak larut yang mungkin terbentuk di dalam produk selama penyimpanan.

Disarankan untuk menggunakan larutan dengan segera setelah diencerkan. ATGAM® yang diencerkan harus disimpan pada suhu ruang (20–25°C) jika tidak segera digunakan. Total waktu dalam keadaan setelah pengenceran tidak boleh melebihi 24 jam (termasuk waktu infus).

Dari sudut pandang mikrobiologi, kecuali jika metode pembukaan dan pengenceran mampu meniadakan risiko kontaminasi mikrobial, produk harus segera digunakan.

ATGAM® harus diperiksa secara visual untuk melihat adanya bahan partikulat dan perubahan warna sebelum diberikan kepada pasien. ATGAM® dapat terlihat bening hingga sedikit keruh, tidak berwarna hingga berwarna merah muda terang atau cokelat muda dan dapat membentuk sedikit endapan berbentuk butiran atau serpihan selama penyimpanan.

Setiap produk yang tidak terpakai atau bahan limbah harus dibuang sesuai persyaratan setempat.

PT. PFIZER INDONESIA
Local Product Document

Generic Name: Equine Anti-Thymocyte Immunoglobulin
Trade Name: ATGAM
CDS Effective Date: 26-Jan-2023
Supersedes: NA

1. NAME OF THE MEDICINAL PRODUCT

ATGAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mL ampoules containing 50 mg Equine Anti-Thymocyte Immunoglobulin per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Transparent to slightly opalescent, colorless to light pink or light brown sterile aqueous solution which may develop a slight granular or flocculus deposit. For dilution prior to administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ATGAM is indicated for use in adults and in children aged 2 years and older for the treatment of acquired moderate to severe aplastic anemia of known or suspected immunologic aetiology as part of standard immunosuppressive therapy in patients who are unsuitable for hematopoietic stem cell transplantation (HSCT) or for whom a suitable HSCs donor is not available.

4.2. Posology and method of administration

Only physicians experienced in immunosuppressive therapy should use ATGAM. Facilities equipped and staffed with adequate laboratory and supportive inpatient medical resources should be used.

Posology

Adult patients and children aged 2 years and older

Dosage recommendations are based on body weight (bw).

The recommended total dose of ATGAM is 160 mg/kg bw, administered as part of standard immunosuppressive therapy, as follows:

- 16 mg/kg bw/day over 10 days or
- 20 mg/kg bw/day over 8 days or
- 40 mg/kg bw/day over 4 days

The recommended infusion duration for the 40 mg/kg dose regimen is 12 to 18 hours. Do not infuse a dose of ATGAM in less than 4 hours.

Monitoring and management of adverse events

Patients should be carefully monitored during and after treatment for adverse events. Recommendations for monitoring and management of adverse events are included in Table 1. Treatment of the adverse events should be instituted in accordance with local guidelines.

Table 1. Recommendations for Monitoring and Management of Adverse Events	
Adverse Event	**Recommendations for Monitoring and Management**
Anaphylaxis, including respiratory distress	To identify those at greatest risk of systemic anaphylaxis, skin testing of potential recipients before commencing treatment is strongly recommended, especially if the patient is atopic. Patients should be carefully monitored for anaphylaxis, including respiratory distress, and treatment should be discontinued if anaphylaxis occurs (see section 4.4).
Cytokine Release Syndrome (CRS)	If CRS occurs, discontinuation of treatment should be considered (see section 4.4).
Thrombocytopenia and neutropenia	If there is evidence of severe and unremitting thrombocytopenia or neutropenia, discontinuation of treatment should be considered (see section 4.4).

Special populations

Renal and hepatic impairment

Specific clinical studies have not been performed to assess the effect of renal or hepatic impairment on the pharmacokinetics of ATGAM.

Paediatric population

Currently available data in children less than 18 years of age are described in section 4.8 and 5.1.

Elderly population (≥65 years of age)

Clinical experience in elderly patients has not identified differences in responses between the elderly and younger patients. Therefore, no dose adjustment is recommended for elderly patients.

Method of administration

Following dilution, ATGAM is intended for intravenous use and administration via a high-flow central vein is preferred.

Monitor the patient continuously throughout the infusion for possible allergic reactions (see sections 4.4 and 4.8). Always keep appropriate resuscitation equipment at the patient's bedside while ATGAM is being administered.

Diluted ATGAM should be at room temperature before infusion (see section 6.6). ATGAM is appropriately administered into a vascular shunt, arterial venous fistula, or a high-flow central vein, using an in-line filter (not supplied) with a pore size of 0.2 to 1.0 micron. The in-line filter should be used with all infusions of ATGAM to prevent the administration of insoluble material that may have developed in the concentrate. The use of high-flow veins will minimize the occurrence of phlebitis and thrombosis.

Infusion volumes of 250 mL to 500 mL may be used. The infusion volume of the diluted solution should take into consideration factors such as patient's hemodynamic status, age, and weight. Following administration, it is recommended to flush the intravenous line.

Treatment of aplastic anemia - concomitant immunosuppressive therapy and pre-medication

ATGAM is most commonly administered with ciclosporin.

It is recommended to administer pre-medication with corticosteroids and antihistamines prior to infusion of ATGAM in accordance with local treatment guidelines. Anti-pyretics may also increase the tolerability of ATGAM infusion (see section 4.4).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to any other Equine Anti-Thymocyte Immunoglobulin preparation.

4.4. Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Only physicians experienced in immunosuppressive therapy should use ATGAM. Facilities equipped and staffed with adequate laboratory and supportive medical resources should be used. Patients should be carefully monitored during and after therapy with ATGAM for adverse events. Treatment of the adverse events should be instituted in accordance with local guidelines.

Special considerations for ATGAM infusion

ATGAM should be administered into a high flow central vein through an in-line filter (not supplied). ATGAM should not be infused in less than 4 hours. Increasing the infusion duration may minimize adverse reactions. The patient should be kept under

continuous observation during and after the infusion for possible allergic reactions (see section 4.8).

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of ATGAM. Clinical signs associated with anaphylaxis, other infusion-associated reactions, and serum sickness and associated symptoms such as rash, arthralgia, pyrexia, chills, and pain have been reported (see section 4.8).

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of ATGAM.

It is recommended to administer corticosteroids and antihistamines prior to infusion of ATGAM (see sections 4.2 and 4.5). Antipyretics may also be administered to increase the tolerability of ATGAM infusion.

Cytokine release syndrome

Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome, which can be fatal (see section 4.2).

Anaphylaxis/skin testing

Discontinue ATGAM if anaphylaxis occurs. To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients is **strongly** recommended before commencing treatment. A conservative, conventional approach would first employ epicutaneous (prick) testing with undiluted ATGAM. If the patient does not show a wheal ten minutes after pricking, proceed to intradermal testing with 0.02 mL of a 1:1000 v/v (volume/volume) saline dilution of ATGAM with a separate saline control injection of similar volume. Read the result at 10 minutes: a wheal at the ATGAM site 3 or more mm larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction should the drug be dosed intravenously.

The predictive value of this test has not been proven clinically. Allergic reactions such as anaphylaxis have occurred in patients whose skin test is negative. Also, skin testing done as described above will not predict for later development of serum sickness. In the presence of a locally positive skin test to ATGAM, serious consideration to alternative forms of therapy should be given. The risk to benefit ratio must be carefully weighed. If therapy with ATGAM is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and a physician familiar with the treatment of potentially life-threatening allergic reactions is in attendance.

Infection

Due to the nature of the immunosuppressive effects of ATGAM, opportunistic infections (bacterial and fungal) are very common. Sepsis has also been reported. There is an increased risk of viral reactivation (e.g., cytomegalovirus [CMV] infection, Epstein–Barr virus [EBV] infection, herpes simplex virus [HSV]). Monitor patients closely for concurrent infection. Some physicians have found that it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents which might be administered concomitantly with ATGAM.

In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind.

Thrombocytopenia and neutropenia

Treatment with ATGAM may exacerbate thrombocytopenia and neutropenia. Consider discontinuing therapy if severe and unremitting thrombocytopenia or leukopenia occurs (see section 4.2).

Renal and liver function tests

In patients with aplastic anemia and other hematologic abnormalities who have received ATGAM, abnormal test results of liver function and renal function have been observed.

Concomitant use of vaccines

The safety and effectiveness of immunisation with vaccines and treatment with ATGAM have not been studied. Vaccination is not recommended in conjunction with ATGAM therapy as the effectiveness of the vaccines could be reduced. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy.

Elderly population

Clinical experience in a limited number of elderly patients (≥65 years of age) has not identified differences in responses between the elderly and younger patients.

Excipients

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per total dose, that is to say is essentially ‘sodium-free’.

ATGAM may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total daily intake from all sources that will be administered to the patient.

Transmissible Agents

ATGAM is made from horse plasma and also employs human blood-derived reagents in the process.

Effective manufacturing steps for the inactivation/removal of viruses are employed in the ATGAM process and these steps have been validated to clear a wide range of both human blood-borne and horse viruses, using a virus panel approach. This covers the complete virus spectrum from small, non-enveloped viruses such as parvoviruses and Hepatitis A to large enveloped viruses like Herpes Simplex Virus. Despite this, when medicinal products prepared from horse and human blood are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

4.5. Interaction with other medicinal products and other forms of interaction

When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to ATGAM may appear. Under these circumstances, monitor patients especially closely during and after therapy with ATGAM.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during and up to 10 weeks after cessation of therapy.

Pregnancy

ATGAM was not teratogenic in rats or monkeys. Studies in animals have shown reproductive toxicity (see section 5.3). These effects are not considered relevant to humans.

There are no adequate and well-controlled studies in pregnant women. There is a limited amount of data from the use of ATGAM in pregnant women. The outcome of pregnancies cannot be determined. ATGAM should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

In animal studies, ATGAM was not detected at the limit of quantification in the milk of lactating cynomolgus monkeys (*Macaca fascicularis*). It is not known whether ATGAM is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-feeding neonates and infants from ATGAM, a decision should be made whether to discontinue breast-feeding or to discontinue the drug taking into account the importance of the drug to the mother.

Fertility

Administration of ATGAM to cynomolgus monkeys (*Macaca fascicularis*) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effect of ability to drive or use machines have been performed. Given the potential adverse reactions that may be experienced (e.g., dizziness, convulsion, confusional state, syncope), caution should be taken when driving or using machinery while on this medication.

4.8. Undesirable effects

The most commonly reported adverse drug reactions (occurring in greater than 10% of patients) are localised infection, infections, neutropenia, serum sickness, headache, hypertension, diarrhoea, abdominal pain upper, nausea, rash, urticaria, arthralgia, chills, pyrexia, pain, oedema and liver function test abnormal.

The adverse drug reactions (ADR) reported with ATGAM during clinical trials or through post marketing experience are presented in the table below. Adverse drug reactions are listed by MedDRA System Organ Class and Preferred Term. Within each System Organ Class, adverse drug reactions are presented in order of decreasing seriousness.

Table 2. Adverse Drug Reactions and Numeric Frequencies and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in Patients with Aplastic Anemia[a]

System Organ Class	ADR Term	Frequency (%)	Category[b]
Infections and infestations	Localised infection	51.8	Very Common
	Infection	20.4	Very Common
	Herpes simplex	2.2	Common
	Sepsis	0.7	Common
	Encephalitis*	-	Not Known
	Systemic infection*	-	Not Known
	Hepatitis viral*	-	Not Known
	Epstein–Barr virus infection*	-	Not Known
	Cytomegalovirus infection*	-	Not Known
Blood and lymphatic system disorders	Neutropenia	21.9	Very Common
	Lymphadenopathy	4.6	Common
	Haemolysis	2.2	Common
	Leukopenia	1.5	Common
	Thrombocytopenia	0.9	Uncommon
	Anaemia*	-	Not Known
	Eosinophilia*	-	Not Known
	Granulocytopenia*	-	Not Known
	Haemolytic anaemia*	-	Not Known
	Pancytopenia*	-	Not Known
Immune system disorders	Serum sickness	16.8	Very Common
	Anaphylactic reaction	0.9	Uncommon
Metabolism and nutrition disorders	Hyperglycaemia	2.2	Common
Psychiatric disorders	Agitation	0.9	Uncommon
	Confusional state*	-	Not Known
	Disorientation*	-	Not Known
Nervous system disorders	Headache	17.4	Very Common
	Dizziness	2.8	Common
	Paraesthesia	2.2	Common
	Seizure	1.8	Common
	Syncope	1.5	Common
	Dyskinesia*	-	Not Known
	Tremor*	-	Not Known
Eye disorders	Periorbital oedema	0.9	Uncommon
Cardiac disorders	Bradycardia	5.5	Common
	Tachycardia	2.9	Common
	Cardiac failure congestive*	-	Not Known
Vascular disorders	Hypertension	12.4	Very Common
	Hypotension	9.2	Common
	Thrombophlebitis	4.6	Common
	Deep vein thrombosis*	-	Not Known
	Iliac vein occlusion*	-	Not Known
	Vasculitis*	-	Not Known

Table 2. Adverse Drug Reactions and Numeric Frequencies and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in Patients with Aplastic Anemia[a]

System Organ Class	ADR Term	Frequency (%)	Category[b]
Respiratory, thoracic and mediastinal disorders	Cough	4.4	Common
	Dyspnoea	4.4	Common
	Pleural effusion	3.7	Common
	Epistaxis	2.9	Common
	Apnoea*	-	Not Known
	Hiccups*	-	Not Known
	Laryngospasm*	-	Not Known
	Oropharyngeal pain*	-	Not Known
	Pulmonary oedema*	-	Not Known
Gastrointestinal disorders	Diarrhoea	13.1	Very Common
	Abdominal pain upper	11.0	Very Common
	Nausea	11.0	Very Common
	Vomiting	7.3	Common
	Abdominal pain	6.6	Common
	Stomatitis	2.9	Common
	Gastrointestinal haemorrhage	1.5	Common
	Gastrointestinal perforation*	-	Not Known
	Oral pain*	-	Not Known
Skin and subcutaneous tissue disorders	Rash	97.2	Very Common
	Urticaria	13.8	Very Common
	Pruritus	5.5	Common
	Dermatitis allergic	0.9	Uncommon
	Toxic epidermal necrolysis*	-	Not Known
	Hyperhidrosis*	-	Not Known
	Night sweats*	-	Not Known
Musculoskeletal and connective tissue disorders	Arthralgia	64.2	Very Common
	Back pain	2.2	Common
	Myalgia	2.2	Common
	Flank pain*	-	Not Known
	Muscle rigidity*	-	Not Known
	Pain in extremity*	-	Not Known
Renal and urinary disorders	Proteinuria	1.8	Common
	Kidney enlargement*	-	Not Known
	Acute kidney injury*	-	Not Known
	Renal artery thrombosis*	-	Not Known
Congenital, familial and genetic disorders	Aplasia*	-	Not Known
General disorders and administration site conditions	Chills	64.2	Very Common
	Pyrexia	51.4	Very Common
	Pain	27.0	Very Common
	Oedema	13.9	Very Common
	Chest pain	4.6	Common
	Malaise	2.2	Common
	Infusion site erythema	0.7	Uncommon
	Asthenia*	-	Not Known
	Infusion site pain*	-	Not Known
	Infusion site swelling*	-	Not Known
Investigations	Liver function test abnormal	19.7	Very Common
	Renal function test abnormal	6.6	Common

Table 2. Adverse Drug Reactions and Numeric Frequencies and Frequency Categories Listed in Order of Decreasing Frequency Within Each System Organ Class Reported in Patients with Aplastic Anemia[a]

System Organ Class	ADR Term	Frequency (%)	Category[b]
Injury, poisoning and procedural complications	Arteriovenous fistula thrombosis*	-	Not Known
	Kidney rupture*	-	Not Known
	Wound dehiscence*	-	Not Known

a. The highest frequency has been reported from aplastic anemia studies from the 1970s (Studies 3-197, 3-198, 5000, 10-20 mg/kg/day, N=109), and pivotal literature studies (Scheinberg 2009 and 2011). 40 mg/kg/day, N=137.
b. CIOMS III categories: Very Common ≥1/10 (≥10%), Common ≥1/100 to <1/10 (≥1% and <10%), Uncommon ≥1/1000 to <1/100 (≥0.1% and <1%), Rare ≥1/10,000 to <1/1000 (≥0.01% and <0.1%), Very Rare <1/10,000 (<0.01%).
* Not known = Frequency not known (cannot be estimated from the available data).

Paediatric population

Data from published studies of differing designs suggest that the safety of ATGAM in paediatric patients with aplastic anaemia is similar to that of adults, when treated with dosages comparable to those used in adults over similar treatment durations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

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

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9. Overdose

The maximum tolerated dose of ATGAM would be expected to vary from patient to patient due the biological nature of the product. The largest single daily dose known to be administered to one patient (renal transplant recipient) was 7000 mg administered at a concentration of approximately 10 mg/mL of saline, seven times the recommended total dose and infusion concentration. In this patient, the administration of ATGAM was not associated with any signs of acute intoxication or late sequelae.

A maximum therapeutic dose has not been established therefore the definition of overdose for ATGAM has not been clearly defined. Some aplastic anaemia patients have received up to 21 doses as additional alternate day therapy for another 14 days. The incidence of toxicologic manifestations did not increase with any of these regimens; however close monitoring of the patient is recommended.

There is no known antidote. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATGAM is composed of antibodies that bind a wide variety of proteins on the surface of lymphocytes. In addition, ATGAM binds to granulocytes, platelets and bone marrow cells. The mechanism of ATGAM -induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocytes. Lymphocyte depletion may be caused by complement dependent lysis and/or activation-induced apoptosis. In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes which results in partial activation and induction of T lymphocyte anergy.

The mechanism of ATGAM therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, ATGAM directly stimulates the growth of HSCs and release of hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony-stimulating factor.

Clinical efficacy and safety

Treatment of aplastic anemia

ATGAM was evaluated in 5 clinical studies that enrolled a total of 332 patients with aplastic anemia who were evaluable for efficacy, including patients who had aplastic anemia of idiopathic or presumed immunologic aetiology and patients with aplastic anemia secondary to other conditions. Of these, 252 patients were treated with ATGAM 160 mg/kg which was administered in equally divided doses over 4 or 8 or 10 days; 115 patients (46%) received ATGAM as the only immunosuppressive agent while CsA was co-administered to 137 patients (54%).

The response rate in individual studies ranged from 39% to 68%, with the higher rates seen in the more recent studies that included CsA (see Table 2). ATGAM has induced instances of partial or complete hematologic recovery and improved survival in patients with aplastic anemia of known or suspected immunologic aetiology in patients who are unsuitable for bone marrow transplant.

160 mg/kg (total dose) administered over 8 or 10 days

Study 3-197, Study 3-198, Study 5000

In 3 controlled clinical studies completed in the 1980's, 115 evaluable patients with moderate (Study 3-197 and Study 5000) to severe (all 3 studies) aplastic anemia who were not candidates for bone marrow transplantation were administered eATG at 160 mg/kg bw over 8 or 10 days; patient ages ranged from 1 to 76 years. Hematologic response rates for eATG-treated patients ranged from 39% to 52% in these three studies, and survival rates were 50% or more. See Table 2 for more details.

160 mg/kg (total dose) administered over 4 days

(Scheinberg 2011)
A total of 120 treatment-naïve patients (60 per arm), with severe aplastic anemia, 2 to 77 years of age, were randomized to receive either eATG at 40 mg/kg bw/day for 4 days or rabbit anti-thymocyte globulin (rATG) at 3.5 mg/kg/day for 5 days. Each treatment arm also included CsA at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) given in divided doses every 12 hours for at least 6 months, with the dose adjusted to maintain trough blood levels of 200 to 400 ng/mL. The primary endpoint was hematologic response at 6 months, defined as no longer meeting the criteria for severe aplastic anemia. The observed rate of hematologic response at 6 months was in favour of eATG compared with rATG (68% vs 37%, respectively [$p< 0.001$]). The overall survival rate at 3 years differed significantly between the two regimens: 96% in the eATG group compared with 76% in the rATG group ($p=0.04$) when data were censored at the time of stem cell transplantation, and 94% compared with 70% ($p=0.008$) in the respective groups when stem cell transplantation events were not censored.

(Scheinberg 2009)
A total of 77 patients with severe aplastic anemia, 4 to 78 years of age, participated in a prospective, randomized study comparing eATG/ciclosporin (CsA)/sirolimus with standard eATG/CsA immunosuppressive therapy. Thirty-five patients received eATG/CsA/sirolimus and 42 patients received standard eATG/CsA. Intravenous eATG was administered at a dose of 40 mg/kg bw/day for 4 days and CsA was given at 10 mg/kg/day (15 mg/kg/day for children under 12 years old) for 6 months. Based on randomization, oral sirolimus was given at 2 mg/day in adults or 1 mg/m^2/day in children less than 40 kg for 6 months. The primary endpoint of the study was hematologic response rate at 3 months, defined as no longer meeting the criteria for severe aplastic anemia.

After a planned interim analysis of 30 evaluable patients in each arm, accrual to the eATG/CsA/sirolimus arm was closed, as the conditional power for rejecting the null hypothesis was less than 1%. The overall response rate at 3 months was 37% for eATG/CsA/sirolimus and 57% for eATG/CsA, and at 6 months was 51% for eATG/CsA/sirolimus and 62% for eATG/CsA. The overall survival at 3 years for patients in the eATG/CsA/sirolimus arm was 97%, and was 90% in the eATG/CsA arm. See Table 3 for more details.

Table 3. Key Clinical Studies with ATGAM for the Treatment of Aplastic Anemia*

Study	eATG+ comparator or other therapy	No. of subjects analysed	Response rate (endpoint)[a]	*P* Value	Survival rate (time point)	*P* Value
160 mg/kg (total dose) administered over 8 days or 10 days						
Study 3-197 (20 mg/kg for 8 days)	eATG	21	47%[b]/ 52%[c] (3 mo)	<0.01[b]/ <0.01[c]	62%[d] (12 mo)	NA
	Supportive care only	20	6%[b]/ 0%[c] (3 mo)			
Study 3-198 (16 mg/kg for 10 days)	eATG + OXY + Bone marrow infusion	23	43%[b]/ 39%[c] (3 mo)	Not reported	83% (12 mo)	=0.14
	eATG + OXY	18	44%[b]/ 39%[c] (3 mo)		59% (12 mo)	
Study 5000 (20 mg/kg for 8 days)	eATG + Androgen	26	42% (6 mo)	>0.9	55%[e] (24 mo)	=0.65
	eATG + Placebo	27	44% (6 mo)		50%[e] (24 mo)	
160 mg/kg (total dose) administered over 4 days						
Scheinberg 2011	eATG + CsA	60	68% (6 mo)	<0.001	96%[g]/94%[h] (36 mo)	=0.04[g]/=0.008[h]
	rATG[f] + CsA	60	37% (6 mo)		76%[g]/70%[h] (36 mo)	
Scheinberg 2009	eATG+ CsA + sirolimus	35	51% (6 mo)	Not reported	97% (36 mo)	=0.30 (log-rank)
	eATG + CsA	42	62% (6 mo)		90% (36 mo)	

Abbreviation: OXY: oxymetholone.
* These clinical studies were conducted from 1979 to 2010.
[a] Hematologic response was defined differently in different studies, confidence intervals added where available.
[b] Sponsor's evaluation of response.
[c] Investigator's evaluation of response.
[d] This survival estimate includes the 21 subjects who were randomized to receive eATG, plus another 11 subjects who received eATG after crossing over from the control group.
[e] Patients with severe aplastic anemia only.
[f] CsA was discontinued at 6 months in the rATG group.
[g] Subjects who had stem cell transplantation were censored.
[h] Subjects who had stem cell transplantation were not censored.

Immunogenicity

Antibody against horse IgG was assessed in two clinical studies performed in renal transplant patients treated with ATGAM; 9% to 37% of treated patients show detectable levels of anti-horse IgG antibodies.

The incidence of anti-horse antibody formation in aplastic anemia patients and of their neutralizing potential is unknown and its clinical significance has not been established.

5.2. Pharmacokinetic properties

Distribution

During infusion of 10 to15 mg/kg/day, the mean peak value (n=27 renal transplant patients) was found to be 727 ± 310 µg/mL.

Metabolism and elimination

The half-life of equine immunoglobulin after ATGAM infusion was found to be 5.7 ± 3.0 days in renal transplant patients. The range for half-life was 1.5 to 13 days.

Pharmacokinetic in special groups of subjects or patients

Ethnicity

A clinical study examined the pharmacokinetics of ATGAM in 6 adult Japanese patients with moderate or severe aplastic anemia. When administered via intravenous infusion at a dose of 10 mg/kg/day (N=3) or 20 mg/kg/day (N=3) for 8 days, the mean concentration was 1180 ± 240 µg/mL and 2060 ± 340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard identified for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity and pre-/post-natal development studies have not been conducted on ATGAM.

Fertility

Administration of ATGAM to cynomolgus monkeys (Macaca fascicularis) at doses comparable to those used in clinical studies was not associated with impairment of male or female fertility.

Pregnancy

ATGAM was not embryotoxic, fetotoxic, or teratogenic in rats, after doses similar to doses used in humans. An increase in hypoplastic cervical vertebrae was observed in rat fetuses at doses of 100 mg/kg/day administered ATGAM during organogenesis.

In cynomolgus monkey (Macaca fascicularis) reproduction studies, ATGAM was embryotoxic and fetotoxic. Maternal toxicity was observed with ATGAM doses of 20 mg/kg/day after 14 days of dosing with maternal deaths occurring at doses of 40 mg/kg/day. Fetal deaths occurred in dams treated with 20 mg/kg/day during the first part of organogenesis, but not in dams treated during the latter part of organogenesis. The maternal and fetal deaths were attributed to maternal anemia due to red blood cell antigen that humans do not share. Therefore, this toxicity is not considered relevant to human fetal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycine
Water for injections
10% solution sodium hydroxide (to adjust pH)
10% solution hydrochloric acid (to adjust pH)

6.2. Incompatibilities

ATGAM must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Diluted solution

Once diluted, ATGAM has been shown to be physically and chemically stable for up to 24 hours at 25°C, at concentrations of up to 4 mg/mL in the following diluents: 0.9% Sodium Chloride Injection, 5% Dextrose and 0.225% Sodium Chloride Injection, and 5% Dextrose and 0.45% Sodium Chloride Injection.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Drug product

Store the drug product in a refrigerator (2°C–8°C). Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

Diluted solution

Diluted solution should be kept at room temperature (25°C). The solution should be used within 24 hours (including infusion time).

6.5. Nature and contents of container

5 mL concentrate for solution in a Type I clear glass ampoule.
Pack size: 5 ampoules.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of infusion solution

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. However, because ATGAM is a gamma globulin product, the ATGAM concentrate and diluted solution are transparent to slightly opalescent, colorless to light pink or light brown sterile aqueous solutions which may develop a slight granular or flocculus deposit.

ATGAM (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

ATGAM concentrate should be diluted for intravenous infusion in an inverted bottle or bag of sterile vehicle, so that the undiluted ATGAM does not contact the air inside

Add the total daily dose of ATGAM to an inverted bottle or bag of one of the following sterile vehicles below:

- 0.9 % sodium chloride solution,
- Glucose solution/sodium chloride solution:
    - 50 mg/mL (5%) glucose in 0.45% (4.5 mg/mL) sodium chloride solution
    - 50 mg/mL (5%) glucose in 0.225% (2.25 mg/mL) sodium chloride solution

Due to possible precipitation of ATGAM, it is not recommended to dilute with glucose solution alone (see section 6.2).

The recommended concentration of the diluted ATGAM is 1 mg/mL in the sterile vehicle. The concentration should not exceed 4 mg/mL of ATGAM.

The diluted solution should be gently rotated or swirled to effect thorough mixing.

7. MARKETING AUTHORISATION HOLDER NAME AND ADDRESS

Manufactured by:
Pharmacia & Upjohn Company LLC
Kalamazoo, Michigan, USA

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER

ATGAM 50 mg/mL concentrate for solution for infusion @ 5 ampoules; No. Reg. DK

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

10/2024

CDS version 7.0