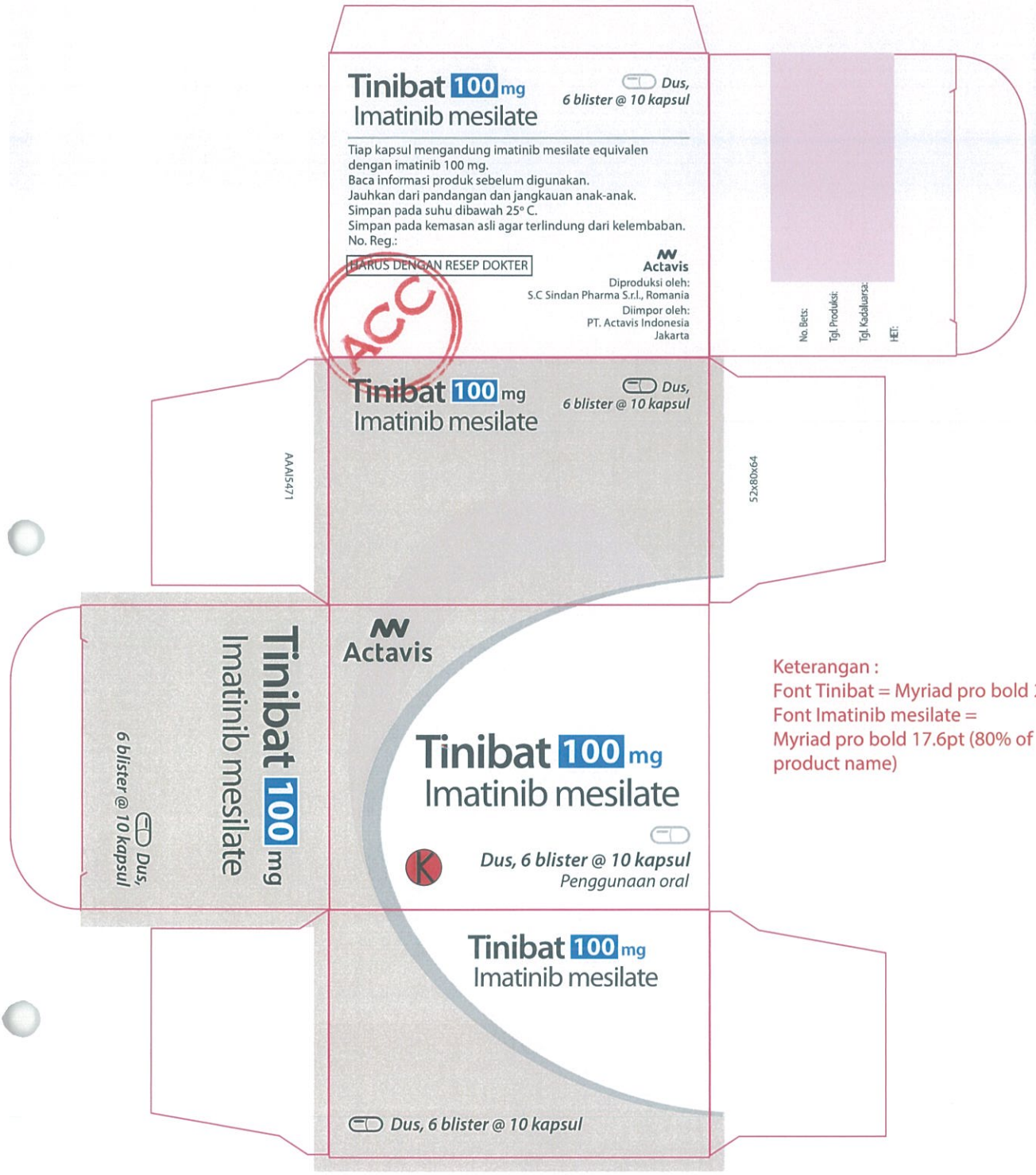

Keterangan :
Font Tinibat = Myriad pro bold 22pt
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Myriad pro bold 17.6pt (80% of product name)

Imatinib 100 mg 60 capsules, Blister carton, Indonesia				colours/plates
actavis	item no: AAAI5471	dimensions: 52x80x64 mm		1. black
@ awstudio@actavis.co.uk	print proof no: 3	pharmacode:		2. pms 877
approved for print/date	origination date: 18.04.2016	min pt size: 7pt		3. warm gray 3
	originated by: KM			4. pms 300
	revision date: 30.11.2017	**Technical Approval**		5. pms 485
	revised by: KM	date sent: 18.04.2016		Non Printing Colours
	supplier: Sindan	technically app. date:		1. Profile
				2. Varnishe free

* Please note the technical approval is provided by the supplier and is valid on the date indicated.
Any technical changes made by the supplier after approval are not the responsibility of the Artwork Studio.

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Imatinib 100 mg -, Blister foil capsules, Indonesia

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creating value in pharmaceuticals

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item no:	AAAI5469
print proof no:	3
origination date:	18.04.2016
originated by:	KM
revision date:	29.07.2019
revised by:	KM
supplier:	Sindan

dimensions:	68x57 mm
pharmacode:	
min pt size: 6pt	

Technical Approval

date sent:	18.04.2016
technically app. date*:	

colours/plates
1. black

Non Printing Colours
1. Profile

* Please note the technical approval is provided by the supplier and is valid on the date indicated.
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Lembar Informasi Obat:
Informasi untuk Pengguna Obat

Tinibat kapsul

Imatinib mesilate

Bacalah seluruh lembar informasi ini dengan seksama sebelum anda mulai mengonsumsi obat ini karena lembar ini berisi informasi penting untuk anda.

- Simpanlah lembar informasi ini. Anda mungkin perlu membacanya lagi.
- Bila anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat anda.
- Obat ini diresepkan hanya untuk anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, meskipun mereka memiliki tanda dan gejala penyakit yang sama dengan anda.
- Bila anda mengalami efek samping obat, bicarakan kepada dokter, apoteker, perawat anda. Termasuk efek samping yang tidak tertulis dalam lembar iniformasi ini.

ACC

Apakah yang terdapat dalam lembar informasi ini:

1. Apakah Tinibat dan digunakan untuk apa

Tinibat adalah obat yang mengandung zat aktif imatinib. Obat ini bekerja menghambat pertumbuhan sel abnormal dalam kanker tipe tertentu.

Tinibat adalah obat dengan indikasi:

- **Leukemia myeloid kronik *(CML)* kromosom philadelphia (bcr-abl) positif (Ph+) yang baru terdiagnosa juga untuk pengobatan CML Ph+ pada fase kronis setelah kegagalan pada terapi interferon-alfa atau pada fase yang dipercepat atau *blast crisis*.** Leukaemia adalah kanker sel darah putih. Sel darah putih ini bekerja membantu tubuh melawan infeksi. Leukimia myeloid kronik adalah bentuk leukimia dimana sel darah putih abnormal tertentu (dinamakan sel myeloid) mulai tumbuh diluar control. Imatinib biasanya digunakan untuk mengobati Leukimia Myeloid Kronik (CML) Ph+ setelah kegagalan dengan terapi interferon-alfa, atau pada fase yang dipercepat atau *blast crisis*.

Tinibat juga obat untuk dewasa dan anak diatas 1 tahun dengan indikasi:

- **Leukimia limfoblastik akut positif kromosom philadelphia/Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph-positive ALL).** Leukaemia adalah kanker sel darah putih. Sel darah putih ini bekerja membantu tubuh melawan infeksi. Leukemia limfoblastik akut adalah

suatu bentuk leukemia dimana sel darah putih abnormal tertentu (yang disebut limfoblas) mulai tumbuh diluar kendali. Tinibat menghambat pertumbuhan sel-sel ini.

Tinibat juga obat untuk dewasa dengan indikasi:

- **Penyakit myelodisplastik/myeloproliferatif (MDS/MPD).** Penyakit ini adalah kelompok penyakit darah dimana beberapa sel darah mulai tumbuh diluar kendali. Tinibat menghambat sel-sel ini pada penyakit dengan subtipe tertentu.
- **Mastositosis sistemik/ Systemic Mastocytosis (SM).** Suatu kelainan yang disebabkan oleh mutasi genetik yang menyebabkan sel mast berkembang terlalu banyak dalam tubuh. Sel mast biasanya membantu melindungi tubuh dari penyakit dan membantu proses penyembuhan luka dengan melepaskan zat-zat seperti histamin dan leukotrien.
- **Sindrom hipereosinofilik/Hypereosinophilic syndrome (HES) dan/atau leukemia eosinofilik kronik/chronic eosinophilic leukaemia (CEL).** Ini adalah penyakit darah dimana beberapa sel darah (yang disebut eosinofil) mulai tumbuh diluar kendali. Tinibat menghambat pertumbuhan berbagai sel ini pada penyakit dengan subtipe tertentu.
- **Dermatofibrosarcoma protuberans (DFSP).** DFSP adalah kanker jaringan bawah kulit dimana beberapa sel mulai tumbuh diluar kendali. Tinibat menghambat pertumbuhan berbagai sel ini. Dalam lembar infomasi ini kami akan menggunakan singkatan ketika membicarakan berbagai penyakit ini.

Bila anda memiliki pertanyaan mengenai bagaimana Tinibat bekerja atau mengapa obat ini diresepkan untuk anda, bicarakan dengan dokter anda.

2. Apakah yang anda perlu ketahui sebelum anda mengonsumsi Tinibat

Tinibat hanya diresepkan untuk anda oleh dokter anda yang telah memiliki pengalaman mengobati kanker darah atau tumor padat.
Ikuti semua instruksi dokter anda dengan seksama, meskipun berbeda dari informasi yang terdapat dalam lembar informasi ini.

Jangan mengonsumsi Tinibat:

- Bila anda alergi terhadap imatinib atau berbagai bahan lainnya yang terkandung dalam obat ini (terdapat dalam bagian 6). Bila hal ini berlaku pada anda, **beritahukan kepada dokter anda dan jangan mengonsumsi Tinibat.** Bila anda berpikir mungkin anda alergi tetapi anda tidak yakin, mintalah saran kepada dokter anda.

Peringatan dan perhatian

Beritahukan kepada dokter anda sebelum anda mengonsumsi Tinibat:

- Bila anda memiliki atau pernah mengalami gangguan hati, ginjal atau jantung.
- Bila anda mengonsumsi levothyroxine karena tiroid anda telah diangkat.
- Bila anda pernah atau mungkin sekarang mengalami infeksi hepatitis B. Ini karena Tinibat dapat menyebabkan hepatitis B menjadi aktif kembali, dimana bisa menjadi fatal pada beberapa kasus. Sebelum dimulai pengobatan, pasien akan dicek secara seksama oleh dokternya untuk tanda-tanda infeksi ini.

Bila anda mengalami berbagai masalah tersebut, **beritahukan kepada dokter anda sebelum anda mengonsumsi Tinibat.**

Selama pengobatan dengan Tinibat, beritahukan kepada dokter anda segera bila anda mengalami peningkatan berat badan yang sangat cepat. Tinibat dapat menyebabkan tubuh anda menahan air (retensi cairan berat).

Ketika anda mengonsumsi Tinibat, dokter anda akan mengecek secara teratur apakah obat bekerja. Anda akan diminta untuk menjalani pemeriksaan darah dan berat badan secara teratur.

Anak dan remaja
Retardasi pertumbuhan terjadi pada anak-anak & pra remaja yang mendapat imatinib. Efek pemakaian jangka panjang imatinib pada pertumbuhan anak belum diketahui. Oleh karena itu, pemantauan ketat pertumbuhan pada anak-anak dengan perawatan imatinib dianjurkan.

Obat-obatan lain dan Tinibat
Beritahukan kepada dokter atau apoteker anda bila anda sedang atau akhir-akhir ini mengonsumsi obat-obatan lain, termasuk obat yang diperoleh tanpa resep dokter (seperti parasetamol) dan termasuk obat herbal (seperti St. John's Wort). Beberapa obat dapat mengganggu efek Tinibat bila dikonsumsi bersamaan. Obat-obatan ini dapat meningkatkan atau menurunkan efek Tinibat, baik mengakibatkan meningkatnya efek samping atau menyebabkan berkurangnya efektivitas Tinibat. Tinibat juga dapat menyebabkan hal yang sama terhadap obat lain.

Beritahukan kepada dokter anda bila anda menggunakan obat yang mencegah terbentuknya bekuan darah.

Hamil, menyusui dan kesuburan
- Bila anda hamil atau menyusui, berpikir bahwa anda mungkin hamil atau merencakan untuk mempunyai anak, mintalah saran kepada dokter anda sebelum anda mengonsumsi obat ini.
- Tinibat tidak direkomendasikan selama kehamilan kecuali sangat dibutuhkan karena obat ini dapat membahayakan bayi anda. Dokter anda akan berdiskusi dengan anda tentang risiko mengonsumsi Tinibat selama kehamilan.
- Perempuan yang mungkin hamil disarankan untuk menggunakan kontrasepsi yang efektif selama pengobatan.
- Jangan menyusui selama pengobatan dengan Tinibat.
- Pasien yang mengkhawatirkan kesuburan mereka ketika mengkonsumsi Tinibat disarankan untuk berkonsultasi dengan dokter.

Mengendarai dan mengoperasikan mesin
Anda mungkin merasa pusing atau mengantuk atau pandangan kabur ketika mengonsumsi obat ini. Bila hal ini terjadi, jangan mengendarai atau mengoperasikan alat atau mesin apapun hingga anda merasa baik kembali.

3. Bagaimana cara mengonsumsi Tinibat

Dokter anda meresepkan Tinibat karena anda mengalami kondisi yang serius. Tinibat dapat membantu anda melawan kondisi ini.

Bagaimanapun juga anda harus selalu konsumsi obat ini tepat sesuai instruksi dokter atau apoteker anda. Penting bahwa anda melaksanakan hal ini selama dokter atau apoteker anda menyarankan demikian. Cek dengan dokter atau apoteker anda bila anda tidak yakin.

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Jangan berhenti mengonsumsi Tinibat kecuali dokter anda menyarankan anda untuk menghentikannya. Bila anda tidak dapat mengonsumsi obat sesuai resep dokter anda atau anda merasa tidak membutuhkannya lagi, hubungi dokter anda segera.

Berapa banyak Tinibat yang harus dikonsumsi

Penggunaan pada dewasa
Dokter anda akan memberitahukan kepada anda berapa banyak kapsul Tinibat yang harus anda konsumsi.

- **Bila anda dalam pengobatan untuk CML:**
  Bergantung pada kondisi anda, dosis awal biasanya adalah 400 mg atau 600 mg:
  - **400 mg** dikonsumsi dalam bentuk 1 kapsul **sekali** sehari,
  - **600 mg** dikonsumsi dalam bentuk 1 kapsul 400 mg plus 2 kapsul 100 mg **sekali** sehari.

- **Bila anda dalam pengobatan untuk Ph-positive ALL:**
  Dosis awal adalah 600 mg, dikonsumsi dalam bentuk 1 kapsul 400 mg plus 2 kapsul 100 mg **sekali** sehari.

- **Bila anda dalam pengobatan untuk MDS / MPD:**
  Dosis awal adalah 400 mg, dikonsumsi dalam bentuk 1 kapsul **sekali** sehari.

- **Bila anda dalam pengobatan untuk SM:**
  Dosis awal adalah 400 mg, dikonsumsi dalam bentuk 1 kapsul **sekali** sehari.

- **Bila anda dalam pengobatan untuk HES / CEL:**
  Dosis awal adalah 100 mg, dikonsumsi dalam bentuk 1 kapsul sekali sehari. Dokter anda dapat meningkatkan dosis hingga 400 mg, yang dikonsumsi dalam bentuk 1 kapsul 400 mg **sekali** sehari, bergantung bagaimana respons anda terhadap pengobatan.

- **Bila anda dalam pengobatan untuk DFSP:**
  Dosis 800 mg per hari (2 kapsul 400 mg), dikonsumsi dalam bentuk 1 kapsul pada pagi hari dan 1 kapsul pada malam hari.

Penggunaan pada anak dan remaja
Belum ada pengalaman penggunaan imatinib untuk anak-anak dengan Ph+ALL usia kurang dari 1 tahun. Data penggunaan imatinib untuk indikasi lain masih terbatas atau hampir tidak ada.

Dokter akan memberitahukan kepada anda berapa banyak kapsul Tinibat yang akan diberikan kepada anak Anda. Jumlah Tinibat yang diberikan bergantung pada kondisi, berat badan dan tinggi badan anak anda.
Dosis harian total untuk anak dan remaja tidak boleh melebihi 800 mg pada anak dengan CML dan 600 mg pada anak dengan Ph+ALL. Pengobatan dapat diberikan kepada anak anda dengan cara satu kali sehari atau dapat terbagi dua kali pemberian (setengah pada pagi hari dan setengah sisanya pada malam hari).

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Kapan dan bagaimana cara mengonsumsi Tinibat

- **Konsumsi Tinibat bersama dengan makanan.** Ini akan membantu melindungi anda dari masalah lambung ketika mengonsumsi Tinibat.
- **Telan kapsul seluruhnya dengan segelas besar air putih.**

Bila anda tidak dapat menelan kapsul, anda dapat membuka kapsul dan tuang bubuk kedalam segelas air putih atau jus apel:

- Gunakan sekitar 50 ml untuk setiap 100 mg kapsul.
- Gunakan sekitar 200 ml untuk setiap 400 mg kapsul.
- Aduk dengan sendok hingga bubuk seluruhnya terlarut.
- Begitu bubuk larut, minum seluruh isi gelas segera. Sisa bubuk terlarut dapat tertinggal di gelas.

Berapa lama harus mengonsumsi Tinibat

Konsumsi Tinibat setiap hari selama dokter anda mengatakan demikian.

Bila anda mengonsumsi Tinibat lebih dari seharusnya

Bila anda secara tidak sengaja mengonsumsi terlalu banyak kapsul, beritahukan kepada dokter anda **segera**. Anda mungkin membutuhkan pertolongan medis. Bawa paket obat bersama dengan anda.

Bila anda terlupa mengonsumsi Tinibat

- Bila anda terlupa satu dosis, konsumsilah segera begitu anda teringat. Tetapi bila telah dekat dengan waktu konsumsi dosis berikutnya, lewatkan dosis yang terlupa tersebut.
- Kemudian lanjutkan dengan jadwal normal anda.
- Jangan konsumsi dosis ganda untuk menggantikan dosis yang terlupa.

Bila anda memiliki pertanyaan lebih lanjut mengenai bagaimana cara mengonsumsi obat ini, bertanyalah kepada dokter, apoteker atau perawat anda.

4. Kemungkinan efek samping obat

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya. Efek samping yang terjadi biasanya ringan hingga sedang.

Beberapa efek samping dapat serius. Beritahukan kepada dokter anda segera bila anda mengalami hal sebagai berikut:

Sangat sering (dapat mempengaruhi lebih dari 1 dari 10 orang) **atau sering** (dapat mempengaruhi hingga 1 dari 10 orang)**:**

- Berat badan meningkat cepat. Tinibat dapat menyebabkan tubuh anda menahan air (retensi cairan berat).
- Tanda-tanda infeksi seperti demam, menggigil berat, sakit tenggorok atau ulkus mulut. Tinibat dapat mengurangi sejumlah sel darah putih, oleh karena itu anda dapat lebih mudah terkena infeksi.
- Perdarahan atau memar yang tidak terduga (ketika anda tidak mengalami perlukaan apapun).
- Nyeri pada otot dan tulang rangka setelah perawatan dihentikan (termasuk nyeri otot, nyeri pada ekstremitas (anggota gerak), nyeri sendi, nyeri tulang, nyeri tulang belakang)

Efek samping yang tidak sering terjadi (dapat memengaruhi hingga 1 dari 100 orang) **atau jarang terjadi** (dapat memengaruhi hingga 1 dari 1.000 orang)**:**

- Nyeri dada, irama jantung tidak teratur (tanda masalah jantung).
- Batuk, sesak napas atau nyeri saat bernapas (tanda masalah paru).
- Merasa kepala ringan, pusing atau pingsan (tanda tekanan darah rendah).
- Merasa sakit (mual), disertai menurunnya nafsu makan, air seni berwarna gelap, kulit atau mata kuning (tanda masalah hati).
- Ruam, kulit merah dengan lecet pada bibir, mata, kulit atau mulut, kulit terkelupas, demam, bentol berwarna merah atau ungu, gatal, rasa terbakar, erupsi pustular (tanda masalah kulit).
- Nyeri perut berat, muntah atau feses atau air seni bercampur darah, feses berwarna hitam (tanda gangguan gastrointestinal).
- Keluaran air seni sangat sedikit, merasa haus (tanda masalah ginjal).
- Merasa sakit (mual) disertai diare dan muntah, nyeri perut atau demam (tanda masalah usus).
- Sakit kepala berat, lemah atau paralisis anggota gerak atau wajah, sulit berbicara, penurunan kesadaran tiba-tiba (tanda masalah sistem saraf seperti perdarahan atau pembengkakan dalam kepala / otak).
- Kulit pucat, merasa lelah dan sesak dan air seni berwarna gelap (tanda rendahnya jumlah sel darah merah).
- Nyeri mata atau penurunan penglihatan, perdarahan pada mata.
- Nyeri pada panggul atau sulit berjalan.
- Ibu jari kaki dan jari-jari terasa kebas atau dingin (tanda sindrom Raynaud).
- Bengkak dan kemerahan pada kulit yang tiba-tiba (tanda infeksi kulit yang disebut selulitis).
- Kesulitan pendengaran.
- Lemah dan kejang otot disertai irama jantung abnormal (tanda berubahnya jumlah natrium dalam darah).
- Memar.
- Nyeri perut disertai rasa mual (nausea).
- Kejang otot disertai demam, air seni merah kecoklatan, nyeri atau lemah otot (tanda masalah otot).
- Nyeri panggul kadang disertai mual dan muntah, dengan perdarahan vaginal yang tidak terduga, merasa pusing atau pingsan karena tekanan darah rendah (tanda masalah dengan indung telur atau rahim anda).

- Mual, sesak napas, irama jantung tidak teratur, air seni keruh, lelah dan / atau nyeri sendi disertai dengan hasil tes laboratorium abnormal (misalnya kadar natrium, asam urat dan kalsium tinggi, kadar fosfor rendah dalam darah).
- Gumpalan darah di pembuluh darah.

Tidak Diketahui (frekuensi tidak dapat dihitung dari data yang tersedia):
- Kombinasi ruam berat yang tersebar merata, merasa mual, kadar sel darah putih tinggi atau kulit atau mata berwarna kuning (Gejala demam kuning/jaundice) disertai sesak, nyeri / rasa tidak nyaman di dada, keluaran air seni sangat menurun dan merasa haus dll (tanda reaksi alergi akibat obat).
- Gagal ginjal kronik.
- Munculnya kembali (kambuh) infeksi hepatitis B bila anda sebelumnya pernah mengalami hepatitis B (infeksi hati).

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Bila anda mengalami hal tersebut diatas, **beritahukan kepada dokter anda segera.**

Efek samping lainnya adalah:
Sangat sering (dapat memengaruhi lebih dari 1 dari 10 orang)**:**
- Sakit kepada atau merasa lelah.
- Merasa mual (nausea), muntah, diare atau gangguan pencernaan.
- Ruam.
- Kram otot atau nyeri sendi, otot atau tulang.
- Bengkak pada sekitar mata kaki atau mata sembab.
- Berat badan bertambah.

Bila berbagai tanda dan gejala diatas dirasakan berat, **beritahukan kepada dokter anda**.

Efek samping yang sering terjadi (dapat memengaruhi hingga 1 dari 10 orang)**:**
- Anoreksia, berat badan turun atau gangguan nafsu makan.
- Merasa pusing atau lemah.
- Sulit tidur (insomnia).
- Keluar kotoran mata disertai gatal, merah dan bengkak (konjungtivitis), mata berair atau penglihatan kabur.
- Perdarahan hidung.
- Nyeri atau bengkak pada perut, kembung, dada rasa terbakar atau konstipasi.
- Gatal.
- Rambut rontok atau menipis yang tidak seperti biasanya.
- Kebas pada tangan atau kaki.
- Sariawan.
- Nyeri sendi disertai bengkak.
- Mulut kering, kulit kering atau mata kering.
- Menurun atau meningkatnya sensitivitas kulit.
- Rasa panas pada wajah (hot flushes), menggigil atau keringat malam.

Bila berbagai tanda dan gejala diatas dirasakan berat, **beritahukan kepada dokter anda.**

Tidak diketahui (frekuensi tidak dapat dihitung dari data yang tersedia):

- Kemerahan dan / atau bengkak pada telapak tangan dan telapak kaki yang disertai dengan rasa kesemutan dan nyeri seperti terbakar.
- Melambatnya pertumbuhan pada anak dan remaja.
- Lesi kulit yang menyakitkan dan/atau melepuh.

Bila berbagai tanda dan gejala diatas dirasakan berat, **beritahukan kepada dokter anda.**

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Melaporkan efek samping

Bila anda mengalami efek samping apapun, bicarakan kepada dokter, apoteker atau perawat anda, termasuk efek samping yang tidak terdapat dalam lembar informasi ini. Anda juga dapat melaporkan efek samping obat secara langsung (lihat detail dibawah ini). Dengan melaporkan efek samping maka anda telah membantu memberikan informasi lebih banyak mengenai keamanan obat ini.

PT. Actavis Indonesia
Jl. Raya Bogor Km. 28
Jakarta 13710
Tel: 021-871 0311
Fax: 021-871 0044
Website: www.actavis.co.id

5. Bagaimana cara menyimpan Tinibat

- Simpanlah obat ini jauh dari penglihatan dan jangkauan anak.
- Jangan konsumsi obat ini setelah tanggal kadaluarsa yang tertulis pada karton.
- Simpan pada suhu dibawah 25°C. Simpan dalam kotak aslinya agar terlindungi dari lembab.
- Jangan gunakan paket yang telah rusak atau terlihat tanda-tanda perusakan
- Jangan buang obat melalui pembuangan air atau pembuangan rumah tangga. Bertanyalah kepada apoteker anda bagaimana cara membuang obat yang tidak anda gunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah kandungan dalam Tinibat

- Zat aktif adalah imatinib (dalam bentuk mesilate). Setiap kapsul mengandung 100 mg dan 400 mg imatinib (dalam bentuk mesilate).
- Bahan lainnya adalah: Kandungan kapsul: cellulose microcrystalline, copovidone, crospovidone, sodium steryl fumarate, silica (colloidal hydrophobe and colloidal anhydrous). Cangkang kapsul: hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172). Tinta cetak: shellac, black iron oxide (E172), propylene glycol, ammonia solution, potassium hydroxide.

Seperti apakah tampilan Tinibat dan apakah isi paket obat

Tinibat 100 mg: Kapsul keras dengan topi kapsul berwarna oranye terang dan badan kapsul berwarna oranye terang dan tulisan 100 mg dengan tinta hitam.
Kapsul berisikan bubuk kuning terang.

Paket obat:
Obat tersedia dalam kotak yang berisikan 60 kapsul

Tinibat 400 mg: Kapsul keras dengan topi kapsul berwarna oranye buram dan badan kapsul berwarna oranye buram dan tulisan 400mg dengan tinta hitam.
Kapsul berisikan bubuk kuning terang.

Paket obat:
Obat tersedia dalam kotak yang berisikan 10 kapsul

Pemegang Otorisasi Pemasaran
Actavis Group PTC ehf.
Reykjavíkurvegur 76-78,
Hafnarfjörður, Iceland

ACC

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Untuk informasi lebih lanjut mengenai obat ini, harap hubungi perwakilan lokal Pemegang Otorisasi Pemasaran.

pendafe

TINIBAT
Capsule

COMPOSITION

Tinibat 100 mg capsules.
Each capsule contains imatinib mesilate equivalent to imatinib 100mg.
Tinibat 400 mg capsules.
Each capsule contains imatinib mesilate equivalent to imatinib 400mg.

ACC

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: protein-tyrosine kinase inhibitor, ATC code: L01XE01

Mechanism of action

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs; Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha dan beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.

Pharmacodynamic properties

Imatinib is a protein-tyrosine kinase inhibitor which potently inhibits the breakpoint cluster region-Abelson (Bcr-Abl) tyrosine kinase at the *in vitro*, cellular and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome-positive chronic myeloid leukemia (CML) and acute lymphoblastic leukaemia (ALL) patients. In colony transformation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inibition of Bcr-Abl positive colonies from CML patients.
In vivo, imatinib shows anti-tumour activity as a single agent in animal models using Bcr-Abl positive tumour cells.
Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF), PDGFR, and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. Constitutive activation of the PDGF receptor or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of MDS/MPD, HES/CEL and DFSP. In addition, consecutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signaling and proliferation of cells driven by dysregulated PDGFR and Abl kinase activity.

Pharmakokinetic properties

Tinibat 100 mg capsule :

A single center, randomized, single dose, laboratory-blinded, two way, crossover comparative bioavailability study was conducted under fed conditions on twenty-four (24) healthy male subjects. The rate and extent of absorption of Tinibat were measured and compared following a single dose (1 x 100 mg) of Tinibat 100 mg capsule and Glivec® 100 mg capsule. The bioavailability of the two formulation of Imatinib is equivalent under fed conditions.
Pharmacokinetic Parameters:
The mean AUC_T were respectively 7378.9 ng·h/mL and 6655.4 ng·h/mL for the Test and Reference formulations. The mean AUC_∞ were respectively 7802.0 ng·h/mL and 7045.5 ng·h/mL for the Test and Reference formulations.

The mean C_{max} were respectively 442.1 ng/mL and 400.8 ng/mL for the Test and Reference formulations.
The Test to Reference AUC_T ratio of geometric LSmeans was 110.64% (90%CI: 107.15 to 114.23%).
Test to Reference AUC_∞ ratio of geometric LSmeans was 110.55% (90%CI: 107.12 to 114.09%).

Test to Reference C_{max} ratio of geometric LSmeans was 110.19% (90%CI: 104.88 to 115.76%).

The result presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled. The Test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} , AUC_∞ and AUC_T were all within the acceptance range of 80.00 to 125.00%.
Therefore the Test formulation (Tinibat 100 mg capsule manufactured by Sindan-Pharma Srl, Romania for Actavis Group PTC ehf., Iceland) is judged to be bioequivalent to the Reference formulation (Glivec 100 mg Hard Capsules, Novartis Europharm Ltd., UK) under fed conditions.

Tinibat 400 mg capsule :
A single center, randomized, single dose, laboratory-blinded, two-way, crossover comparative bioavailability study was conducted under fed conditions on twenty-three (23) healthy male subjects. The rate and extent of absorption of Tinibat were measured and compared following a single dose (1 x 400 mg) of Tinibat 400 mg capsule and Glivec 400 mg tablet Film Coated Tablets. The bioavailability of the two formulation of Imatinib is equivalent under fed conditions.
Pharmacokinetic Parameters:
The mean AUC_T were respectively 34065.2 ng·h/mL and 35122.9 ng·h/mL for the Test and Reference formulations. The mean AUC_∞ were respectively 35047.8 ng·h/mL and 36086.8 ng·h/mL for the Test and Reference formulations.

The mean C_{max} were respectively 1925.4 ng/mL and 2036.2 ng/mL for the Test and Reference formulations.
The Test to Reference AUCT ratio of geometric LSmeans was 96.44% (90%CI: 92.70 to 100.33%).
Test to Reference AUC_∞ ratio of geometric LSmeans was 96.52% (90%CI: 92.77 to 100.43%).

Test to Reference C_{max} ratio of geometric LSmeans was 94.12% (90%CI: 89.50 to 98.97%).

The result presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled. The Test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max}, AUC_{∞} and AUC_T were all within the acceptance range of 80.00 to 125.00%.
Therefore the Test formulation (Tinibat 400 mg capsule manufactured by Sindan-Pharma Srl, Romania for Actavis Group PTC ehf., Iceland) is judged to be bioequivalent to the Reference formulation (Glivec 400 mg film coated tablets, Novartis Pharma GmbH, Germany) under fed conditions.

THERAPEUTIC INDICATIONS

- Treatment of patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) as well as for treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Treatment of adult and pediatric above 1 year of age patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Treatment of adult patients with:
  - Relapsed or refractory Ph+ ALL as monotherapy;
  - Myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements;
  - Systemic mastocytosis (SM) without the D816V c-Kit mutation or with c-Kit mutational status unknown;
  - Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL);
  - Unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

The effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematologic and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in SM, HES/CEL, and on objective response rates in DFSP. Increased survival in controlled trials has been demonstrated only in newly diagnosed chronic phase CML.

POSOLOGY AND METHOD OF ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.
The prescribed dose should be administered orally with a meal and a large glass of water to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a daily dose of 800 mg should be administered as 400 mg twice a day, in the morning and in the evening.
For patients unable to swallow the capsules, the capsules may be dispersed in a glass of water or apple juice. The required number of capsules should be placed in the appropriate volume of beverage (approximately 50 mL for a 100-mg capsule and 200 mL for a 400-mg capsule) and stirred

with a spoon. The suspension should be administered immediately after complete disintegration of the capsule(s).

Treatment should be continued as long as the patient continues to benefit.

Monitoring of response to imatinib therapy in Ph+ CML patients should be performed routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

Dosage in CML:
Recommended dose: 400 mg/day for adult patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis.
Dose increase from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg daily in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response.
Patients should be monitored closely following dose escalation given the potential for an increased incidence of adverse reactions at higher dosages.

Dosage in Ph+ ALL:
Recommended dose: 600 mg/day for adult patients with Ph+ ALL.
See section on special populations for children.

Dosage in MDS/MPD:
Recommended dose: 400 mg/day for adult patients with MDS/MPD.

Dosage in SM:
Recommended dose: 400 mg/day for adult patients with SM without the D816V c-Kit mutation or mutational status unknown or not responding satisfactorily to other therapies.
For patients with SM associated with eosinophilia, a clonal haematological disease related to the fusion kinase F1P1L1-PDGFR-alpha, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in HES/CEL:
Recommended dose: 400 mg/day for patients with HES/CEL.
For HES/CEL patients with demonstrated FIP1L1-PDGFR-alpha fusion kinase, a starting dose of 100mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be

considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Dosage in DFSP:
Recommended dose: 800 mg/day for adult patients with DFSP.

Dose adjustment for adverse drug reactions:

Non-haematological adverse drug reactions:
If a severe non-haematological adverse reaction develops with imatinib use, treatment must be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.
If elevations in bilirubin > 3 x the institutional upper limit of normal (IULN) or in liver transaminases > 5 x the IULN occur, Imatinib should be withheld until bilirubin levels have returned to a < 1.5 x the IULN and transaminase levels to < 2.5 x IULN. Treatment with Imatinib may then be continued at a reduced daily dose. In adults the dose should be reduced from 400 to 300 mg or from 600 to 400 mg or from 800 mg to 600 mg.

Haematological adverse drug reactions:
Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.

Dose adjustments for neutropenia and thrombocytopenia		
SM Associated with eosinophilia and HES/CEL with FIP1L1-PDGFR-alpha fusion kinase (starting dose 100 mg)	ANC < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop Imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse reaction).
Chronic phase CML, MDS/MPD, SM, and HES/CEL (starting dose 400 mg)	ANC < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop Imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with Imatinib at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and resume Imatinib at reduced dose of 300 mg.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)[c]	[a]ANC < 0.5 x 10^9/L and/or platelets < 10 x 10^9/L	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of Imatinib to 400 mg[b]. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg[d]. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia,

		stop Imatinib until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L, then resume treatment at 300 mg[d].
DFSP (starting dose 800 mg)	ANC < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop Imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume treatment with Imatinib at 600 mg. 3. In the event of recurrence of ANC < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L, repeat step 1 and resume Imatinib at reduced dose of 400 mg.
ANC = absolute neutrophil count [a] occurring after at least 1 month of treatment [b] or 260 mg/m2 in children [c] or 340 mg/m2 in children [d] or 200 mg/m2 in children		

Special populations

Children: There is no experience with the use of Imatinib in children with Ph+ALL below 1 year of age. There is very limited to no experience with the use of Imatinib in children in other indications. Dosing in children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase and advanced phase Ph+ALL (not to exceed the total dose of 600 mg daily). The treatment can be given as a once daily dose in Ph+ALL.

Hepatic insufficiency: Imatinib is mainly metabolized through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections Warnings and Precautions and Adverse drug reactions).

Renal insufficiency: Imatinib and its metabolites are not significantly excreted via the kidney. Since the renal clearance of imatinib is negligible, a decrease in free drug clearance is not expected in patients with renal insufficiency. Patients with mild or moderate renal dysfunction should be given the minimum recommended dose of 400 mg daily as starting dose. Although very limited information is available, patients with severe renal dysfunction or on dialysis could also start at the same dose of 400 mg. However, in these patients caution is recommended. The dose can be reduced if not tolerated or increased for lack of efficacy (see section Warning and Precautions).

Elderly patients: No significant age related pharmacokinetic differences have been observed in adult patients. No specific dose recommendation is necessary in the elderly.

CONTRAINDICATIONS

Use in patients with a hypersensitivity to the active substance or to any of the excipients is contraindicated.

WARNINGS AND PRECAUTIONS

Imatinib should be taken with food and a large glass of water to minimize the risk of gastrointestinal disturbances.
When Imatinib is co-administered with other medicinal products, there is a potential for drug interactions.

Hypothyroidism
Hypothyroidism occurs in thyroidectomy patients undergoing levothyroxine replacement during treatment with Imatinib. Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.

Hepatotoxicity
In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see section Dosage and administration & Adverse drug reactions).
When Imatinib is combined with high-dose chemotherapy regimens, transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been uncommon reports of acute liver failure. Monitoring of hepatic function is recommended in circumstances where Imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see section Adverse drug reactions).

Fluid retention
Occurrences of severe fluid retention (pleural effusion, edema, pulmonary edema, ascites, superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking imatinib. Therefore, it is recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary, appropriate supportive care and therapeutic measures should be undertaken. There was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease.

Patients with cardiac disease or renal failure
Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.
In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Imatinib therapy. The condition was reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Imatinib.
Myelodysplastic (MDS)/myeloproliferative (MPD) diseases and systemic mastocytosis might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or SM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1–2 mg/kg) for 1 - 2 weeks concomitantly with Imatinib should be considered at the initiation of therapy.

Gastrointestinal haemorrhage

In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI hemorrhage, occurred in post-marketing experience in patients with CML, ALL and other disease. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with imatinib. When needed, imatinib discontinuation may be considered (see section adverse drug reactions).

Standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.

Tumor lysis syndrome

Cases of tumor lysis syndrome (TLS) occurred in patients treated with Imatinib. Due to possible occurrences of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Imatinib (see section Adverse drug reactions).

Laboratory tests

Complete blood counts must be performed regularly during therapy with Imatinib. Treatment of CML patients with Imatinib has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is dependent on the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with Imatinib may be interrupted or the dose be reduced, as recommended in Posology & method of administration.

Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving Imatinib. As recommended in section posology and method of administration, non-haematological adverse drug reactions, these laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Imatinib.

Imatinib and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCl) is known to decrease with age, and age did not significantly affect Imatinib kinetics. In patients with impaired renal function, Imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an Imatinib-binding protein, in these patients. There is no correlation between Imatinib exposure and the degree of renal impairment, as classified by the measurement of creatinine clearance (CrCl), between patients with mild (CrCl: 40-59 ml/min) and severe (CrCl: <20 ml/min) renal impairment. However, as recommended in the section Posology and method of administration, the starting dose of Imatinib can be reduced if not tolerated.

Children and adolescents

Growth retardation occurring in children and pre-adolescents receiving Imatinib. The long term effects of prolonged treatment with Imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under Imatinib treatment is recommended (see section Adverse drug reactions).

INTERACTIONS

Observed interactions resulting in a concomitant use not recommended

Drugs that may decrease imatinib plasma concentrations:
Substances that are inducers of CYP3A4 activity could increase metabolism and decrease Imatinib plasma concentration. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to Imatinib. Plasma AUC for imatinib will decrease in patients with malignant gliomas treated with Imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital and pirimidone. Concomitant administration of Imatinib and a product containing St. John's wort led to a reduction in the AUC of Imatinib. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Other interactions that may affect exposure to Imatinib or other drugs

Drugs that may increase Imatinib plasma concentrations:
Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase imatinib concentrations. Caution should be taken when administering Imatinib with inhibitors of the CYP3A4 family.

Drugs that may have their plasma concentration altered by Imatinib:
Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate), indicating an inhibition of the CYP3A4 by Imatinib. Therefore, caution is recommended when administering Imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine or pimozide). Imatinib may increase plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).
Imatinib also inhibits CYP2C9 and CYP2C19 activity in vitro. PT prolongation was observed following co-administration with warfarin. When giving coumarins, short-term PT monitoring is therefore necessary at the start and end of Imatinib therapy and when altering the dosage. Alternatively, the use of low-molecular weight heparin should be considered.
In vitro, Imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol Cmax and AUC being increased. Co-administration of Imatinib with CYP2D6 substrates, such as, metoprolol does not seem to be a risk factor for drug-drug interactions and dose adjustment may not be necessary.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of childbearing potential
Women of childbearing potential must be advised to use highly effective contraception during treatment. Highly effective contraception is a method of birth control which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

Pregnancy
There are no adequate data on the use of Imatinib in pregnant women. There have been post-market reports of spontaneous abortions and infant congenital anomalies from women who have taken Imatinib. Imatinib should be used during pregnancy only if the expected benefit outweighs the potential risk to the fetus. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus.

Breast-feeding
Both Imatinib and its active metabolite can be distributed into human milk. Since the effects of low-dose exposure of the infant to Imatinib are unknown, women taking Imatinib should not breast-feed.

Fertility
There are no data on male patients receiving Imatinib and its effect on male fertility and spermatogenesis. Male patients concerned about their fertility on Imatinib treatment should consult with their physician.

Effects on ability to drive and use machines
Reports of motor vehicle accidents have been received in patients receiving Imatinib. While most of the reports are not suspected to be caused by Imatinib, patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Imatinib. Therefore, caution should be recommended when driving a car or operating machinery.

ADVERSE DRUG REACTIONS
The most frequently reported ADRs were neutropenia, thrombocytopenia, anemia, headache, dyspepsia, edema, weight increased, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain.
The differences in safety profile between Ph+ leukaemias and solid tumours are a higher incidence and are probably due to disease-related factors. Myelosuppression, gastrointestinal adverse events, edema, and rashes are common between these two patients populations. Other GI conditions, such as gastrointestinal obstruction, perforation and ulceration appear to be more indication-specific. Other prominent adverse events that have been observed after exposure to Imatinib, and which may be causally related, include hepatotoxicity, acute renal failure, hypophosphatemia, severe respiratory adverse reactions, tumor lysis syndrome and growth retardation in children.

Depending on the severity of events, dose adjustment may be required. In very few cases will the medication have to be discontinued based on ADRs.

Adverse reactions (Table 2 and Table 3) are ranked under headings of frequency, the most frequent first, using the following convention: *Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, <1/1000); very rare (<1/10,000), including isolated reports.*

Table 2 Adverse Reactions related with CML	
Infections and infestations	
Uncommon	Herpes zoster, herpes simplex, nasopharyngitis, pneumonia[1], sinusitis, cellulitis, upper respiratory tract infection, influenza, urinary tract infection, gastroenteritis, sepsis.
Rare	Fungal infection
Blood and lymphatic system disorders	
Very common	Neutropenia, thrombocytopenia, anaemia.
Common	Pancytopenia, febrile neutropenia.
Uncommon	Thrombocythaemia, lymphopenia, bone marrow depression, eosinophilia, lymphadenopathy.
Rare	Haemolytic anaemia
Metabolism and nutrition disorders	
Common	Anorexia.
Uncommon	Hypokalaemia, increased appetite, hypophosphataemia, decreased appetite, dehydration, gout, hyperuricaemia, hypercalcaemia, hyperglycaemia, hyponatraemia.
Rare	Hyperkalaemia, hypomagnesaemia
Psychiatric disorders	
Common	Insomnia.
Uncommon	Depression, decreased libido, anxiety.
Rare	Confusional state
Nervous system disorders	
Very common	Headache
Common	Dizziness, paraesthesia, taste disturbance, hypoaesthesia.
Uncommon	Migraine, somnolence, syncope, peripheral neuropathy, memory impairment, sciatica, restless leg syndrome, tremor, cerebral hemorrhage.
Rare	Increased intracranial pressure, convulsions, optic neuritis.
Eye disorders	
Common	Eyelid oedema, lacrimation increased, conjunctival haemorrhage, conjunctivitis, dry eye, blurred vision.
Uncommon	Eye irritation, eye pain, orbital oedema, scleral haemorrhage, retinal haemorrhage, blepharitis, macular oedema.
Rare	Cataract, glaucoma, papilloedema.
Ear and labyrinth disorders	
Uncommon	Vertigo, tinnitus, hearing loss
Cardiac disorders	
Uncommon	Palpitations, tachycardia, congestive cardiac failure[2], pulmonary oedema.
Rare	Arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion.
Vascular disorders[3]	
Common	Flushing, hemorrhage.
Uncommon	Hypertension, hematoma, subdural hematoma, peripheral coldness,

	hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, epistaxis, cough.
Uncommon	Pleural effusion[4], pharyngolaryngeal pain, pharyngitis.
Rare	Pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary hemorrhage
Gastrointestinal disorders	
Very common	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain
Common	Flatulence, abdominal distension, gastro-oesophageal reflux, constipation, dry mouth, gastritis.
Uncommon	Stomatitis, mouth ulceration, gastrointestinal haemorrhage, eructation, melaena, oesophagitis, ascites, gastric ulcer, haematemesis, cheilitis, dysphagia, pancreatitis.
Rare	Colitis, inflammatory bowel disease, ileus.
Hepatobiliary disorders	
Common	Increased hepatic enzymes.
Uncommon	Hyperbilirubinaemia, hepatitis, jaundice.
Rare	Hepatic failure[6], hepatic necrosis[6].
Skin and subcutaneous tissue disorders	
Very common	Periorbital oedema, dermatitis/eczema/rash,
Common	Pruritus, face oedema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction.
Uncommon	Rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, dermatitis exfoliative, onychoclasis, folliculitis, petechiae, psoriasis, purpura, skin hyperpigmentation, bullous eruptions.
Rare	Acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discolouration, angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	
Very common	Muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain[5].
Common	Joint swelling.
Uncommon	Joint swelling and muscle stiffness.
Rare	Muscular weakness, arthritis.
Renal and urinary disorders	
Uncommon	Renal pain, haematuria, renal failure acute, urinary frequency increased
Reproductive system and breast disorders	
Uncommon	Gynaecomastia, erectile dysfunction, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, breast enlargement, scrotal oedema
General disorders and administration site conditions	
Very common	Fluid retention and oedema, fatigue.
Common	Weakness, pyrexia, anasarca, chills, rigors.
Uncommon	Chest pain, malaise.
Investigations	
Very common	Weight increased
Common	Weight increased
Uncommon	Blood creatinine increased, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased.

Rare	Blood amylase increased.

1 Pneumonia was reported most commonly in patients with transformed CML.
2 On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML than in patients with chronic CML..
3 Bleeding (haematoma, haemorrhage) was most common in patients with transformed CML (CML-AP and CML-BC).
4 Pleural effusion more commonly in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML.
5 Musculoskeletal pain and related events were commonly observed in patients with CML.
6 Some fatal cases of hepatic failure and of hepatic necrosis have been reported.

Table 3 Adverse reactions from Post-marketing reports	
Nervous system disorders	
Uncommon	Cerebral oedema
Eye disorders	
Rare	Vitreous hemorrhage
Cardiac disorders	
Rare	Pericarditis, carrier tamponade
Vascular disorders	
Uncommon	Thrombosis/embolism
Very rare	Anaphylactic shock
Respiratory, thoracic and mediastinal disorders	
Uncommon	Acute respiratory failure[1], interstitial lung disease
Gastrointestinal disorders	
Uncommon	Ileus/intestinal obstruction, tumor haemorrhage/tumor necrosis, gastrointestinal perforation[2]
Rare	Diverticulitis, gastric antral vascular ectasia (GAVE)
Skin and subcutaneous disorders	
Uncommon	Palmar-plantar erythrodysaesthesia syndrome,
Rare	Liechenoid keratosis, lichen planus.
Very rare	Toxic epidermal necrolysis.
Not known	Drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Rare	Avascular necrosis/hip osteonecrosis, rhabdomyolisis/myopathy.
Not known	Growth retardation in children.
Reproductive disorders	
Very rare	Haemorrhagic corpus luteum/haemorrhagic ovarian cyst
Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Rare	Tumour lysis syndrome
Infections and infestations	
Not known	Hepatitis B reactivation
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain, spinal pain)

[1] Fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions
[2] Some fatal cases of gastrointestinal perforation have been reported

Description of Selected Adverse Drug Reactions

Myelosuppression

Myelosuppression is very common in cancer patients treated with Imatinib. Myelosuppression, thrombocytopenia, neutropenia and anemia were the most frequently occurred Grade 3 and 4

laboratory abnormalities. Overall, the myelosuppression experienced with Imatinib in CML patients was generally reversible and in most patients did not result in dose interruption or dose reduction. Few patients required drug discontinuation. Other events of pancytopenia, lymphopenia and bone marrow depression have also occurred.
Hematologic depression appeared greatest at the highest doses and also appeared to be dependent on stage of CML disease, with Grade 3 or 4 neutropenia and thrombocytopenia between 4 and 6 times higher in blast and accelerated phase as compared to newly diagnosed patients in CP CML. These events can usually be managed with either a reduction of the dose or an interruption of treatment with imatinib, but rarely require discontinuation. The incidence of hematologic toxicities is less in patients with solid tumours than in patients with Ph+ leukemias, with Grade 3/4 neutropenia and thrombocytopenia.

Hemorrhage
CNS and GI hemorrhages are not uncommon in CML patients with compromised marrow function at baseline. Hemorrhages are well-recognized part of disease complications in an acutely ill population of leukemia patients, and may result from thrombocytopenia, or less commonly, platelet dysfunction. However, not all patients experiencing CNS and GI hemorrhages during therapy with Imatinib are thrombocytopenic.
The most common manifestation of clinically significant bleeding was GI hemorrhage, which occurred most commonly in advanced CML patients, where bleeding might occur as part of the underlying disease due to tumor bleeding from tumor hemorrhage/tumor necrosis. In first line CML, the observed frequencies of GI hemorrhage were generally the lowest. Gastric antral vascular ectasia (GAVE) is also rarely occurred in the post marketing setting.

Edema and fluid retention
Edema is a common toxicity of Imatinib appearing in most of the patients across all indications. Edema is dose-related and there appears to be a correlation with its occurrence and plasma levels. The most common manifestation is periorbital edema and somewhat less common is lower extremity edema. Specific therapy is not usually required. Other fluid retention events occur much less commonly, but due to the location of the anatomic site may be potentially serious. The most frequent fluid retention event was pleural effusion, most commonly observed in advanced CML. The frequency of cardiac failure was generally low in patients with edema and fluid retention. It was higher in advanced CML than in other groups. This could be explained by the worse medical condition of advanced CML patients. The same trend was observed for renal failure in patients with edema and fluid retention. Most patients with edema and fluid retention were elderly (>65 years old).
The frequency of events suggesting congestive heart failure was higher on Imatinib than on IFN-alpha in patients with newly-diagnosed in CML. The frequency was appreciably higher in patients with transformed CML (accelerated phase or blast crisis), higher age, or with a baseline hemoglobin of less than 8 g/dL. Congestive Heart Failure (CHF) and left ventricular dysfunction have since been continuously monitored in the PSUR. Across all indications a higher frequency of CHF events observed in patients with CML might indicate differences of some of these disease-related risk factors.

Skin Rashes and Severe Cutaneous Adverse Reactions

A generalized erythematous, maculopapular, pruritic skin rash that can fade despite continued therapy, has been occurred. Some patients may have pruritus without accompanying rash, and sometimes there is an exfoliative component. Re-exposure in some patients has resulted in reappearance of rash, but not in all patients. These eruptions generally respond to antihistamines and topical steroids. Occasionally, systemic steroids are required.

Skin rashes have been observed in up to one third of patients treated with Imatinib across all indications. These are frequently pruritic and most commonly appear as erythematous, maculopapular lesions on the forearm, the trunk or the face. Skin biopsies have revealed a toxic drug reaction with a mixed cellular infiltrate. Although most rashes are mild and self-limiting more severe cases may require interruption or discontinuation of treatment.

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur, and has been observed. LFT abnormalities usually consisted of mild elevations in transaminases, although a minority of patients had elevated levels of bilirubin. Onset is generally within the first two months of therapy, but has occurred as late as 6 to 12 months after commencing therapy. The levels generally normalize after withholding therapy for 1 to 4 weeks.

Hypophosphatemia

Low serum phosphate and hypophosphatemia (up to Grade 3/4) has been observed relatively commonly across all indications, however the origin and the clinical significance of this finding have not been established. Imatinib has been shown to inhibit the differentiation of human monocytes into osteoclasts. The decrease was accompanied by a decrease in the resorptive capacity of these cells. A dose-dependent decrease of RANK-L was observed in osteoclasts in the presence of Imatinib. Sustained inhibition of osteoclastic activity may lead to counter regulatory response resulting in increased levels of PTH. The clinical relevance of the preclinical findings is yet unclear and an association with skeletal AEs such as bone fractures has not been demonstrated.

Gastrointestinal Obstruction, Perforation or Ulceration

GI ulceration, which may represent in extreme cases local irritation by Imatinib, has been observed in a small proportion of patients across all indications.

Tumor lysis syndrome

A causal relationship between tumor lysis syndrome and Imatinib treatment is deemed possible, although some cases were confounded by concomitant medications and other independent risks (see section Warning & Precautions).

Growth retardation in children

Imatinib appears to affect the stature of children, especially children who are pre-pubertal. A causal relationship between growth retardation in children and Imatinib treatment could not be ruled out

although for some cases of growth retardation there was limited information (see section Warning & Precautions).

Severe respiratory adverse drug reaction

Severe respiratory events, sometimes fatal, have been observed with Imatinib treatment, including acute respiratory failure, pulmonary hypertension, interstitial lung disease and pulmonary fibrosis. Pre-existing cardiac or pulmonary conditions that may be associated with severe respiratory events occurred.

Laboratory test abnormalities

Haematology

In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg. However, the occurrence of cytopenias was also clearly dependent on the stage of the disease. In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients. The frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 10^9/L) and thrombocytopenias (platelet count < 50 x 10^9/L) being between 4 and 6 times higher in blast crisis and accelerated phase as compared to newly diagnosed patients in chronic phase CML. In newly diagnosed chronic phase CML grade 4 neutropenia (ANC < 0.5 x 10^9/L) and thrombocytopenia (platelet count < 10 x 10^9/L) were rarely occurred. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.

Biochemistry

Severe elevation of transaminases or bilirubin may occur in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in CML patients.

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal.

OVERDOSE

Experience with higher than therapeutic doses is limited. Isolated cases of Imatinib overdose have been reported. Generally the reported outcome in these cases was improvement or recovery. In the event of overdose the patient should be observed and appropriate symptomatic treatment should be given.

Adult overdose:

1200 to 1600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhoea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.
1800 to 3200 mg (as high as 3200 mg daily for 6 days): Weakness, myalgia, increased creatine phosphokinase, increased bilirubin, gastrointestinal pain.
6400 mg (single dose): nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.
8 to 10 g (single dose): Vomiting and gastrointestinal pain.

ACC

Paediatric overdose
Paediatric exposed to a single dose of 400 mg experienced vomiting, diarrhoea, anorexia and paediatric exposed to a single dose of 980 mg dose experienced decreased white blood cell count and diarrhoea.

STORAGE
Store below 25°C
Store in the original package in order to protect from moisture.

Presentation
Tinibat 100 mg Capsule
Box, 6 blisters @ 10 capsules
No. Reg.: DKI

Tinibat 400 mg Capsule
Box, 1 blister @ 10 capsules
No. Reg.: DKI

HARUS DENGAN RESEP DOKTER

Actavis

Manufactured by
S.C Sindan-Pharma S.r.l
Romania

Imported by
PT Actavis Indonesia
Jakarta