NOVARTIS

TASIGNA® (nilotinib)

Kapsul keras 150 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM : 04/05/2022

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Bacalah brosur ini dengan seksama sebelum Anda mengkonsumsi TASIGNA

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter, apoteker atau tenaga profesional kesehatan Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Apabila Anda mengalami efek samping yang serius, atau Anda mengalami efek samping yang tidak tercantum dalam brosur ini, segera hubungi dokter, apoteker atau tenaga profesional kesehatan Anda.

Daftar isi

1. Apakah TASIGNA dan apa kegunaannya

Apakah TASIGNA itu

TASIGNA merupakan obat yang mengandung nilotinib sebagai zat aktif.

Apakah kegunaan TASIGNA

TASIGNA 150 mg diindikasikan untuk pengobatan pasien dewasa yang baru didiagnosa *Philadelphia chromosome positive chronic myeloid (Ph+ CML)* pada fase kronis. *CML* merupakan sejenis kanker darah yang mengakibatkan tubuh memproduksi terlalu banyak sel darah putih yang abnormal.

Bagaimana cara kerja TASIGNA

Pada pasien CML, terjadi perubahan pada DNA (suatu materi genetis) yang menimbulkan sinyal yang memberitahukan tubuh untuk memproduksi sel darah putih yang abnormal. TASIGNA bekerja dengan cara menghambat sinyal ini sehingga menghentikan produksi sel-sel darah putih yang abnormal.

Cara memonitor pengobatan TASIGNA

Dokter Anda akan memonitor kondisi Anda secara rutin untuk mengecek apakah pengobatan tersebut menghasilkan efek yang diharapkan.

Anda akan mendapatkan tes rutin termasuk tes darah selama pengobatan. Tes ini akan memonitor:

- Jumlah sel darah (sel darah putih, sel darah merah dan platelet)
- Fungsi pankreas dan hati untuk melihat bagaimana toleransi tubuh Anda terhadap TASIGNA
- Jumlah elektrolit di tubuh Anda (kalium, magnesium); elektrolit ini berperan penting dalam fungsi jantung
- Kadar gula dan lemak dalam tubuh Anda.

Anda juga akan mendapatkan pengecekan detak jantung menggunakan mesin yang mengukur aktifitas listrik pada jantung (tes tersebut disebut dengan “ECG”).

Dokter Anda akan mengevaluasi pengobatan Anda secara rutin dan memutuskan apakah Anda harus melanjutkan pengobatan dengan TASIGNA. Jika dokter Anda menyarankan untuk menghentikan pengobatan dengan TASIGNA, dokter Anda akan memonitor CML Anda dan akan menyarankan untuk memulai kembali pengobatan dengan TASIGNA jika kondisi Anda mengindikasikan kebutuhan untuk memulai kembali pengobatan dengan TASIGNA.

Tanyakan kepada dokter Anda, jika Anda memiliki pertanyaan mengenai cara kerja atau mengapa Anda diresepkan TASIGNA.

2. Apa yang harus diketahui sebelum dan selama mengkonsumsi TASIGNA

Ikuti instruksi dokter Anda secara hati-hati karena dapat berbeda dengan informasi umum yang tertera pada brosur ini.

Jangan mengkonsumsi TASIGNA

- Jika Anda mengalami alergi (hipersensitivitas) terhadap nilotinib atau terhadap kandungan zat lain yang terdapat pada TASIGNA.

Jika ada kondisi diatas yang berlaku untuk Anda, **jangan mengkonsumsi TASIGNA dan beritahukan kepada dokter Anda.**

Jika Anda merasa mengalami reaksi alergi, **jangan mengkonsumsi TASIGNA dan beritahukan kepada dokter Anda.**

Perhatian khusus saat mengkonsumsi TASIGNA

- Jika Anda pernah mengalami masalah kardiovaskular seperti serangan jantung, nyeri pada dada (angina), masalah pada peredaran darah otak (stroke), atau masalah pada peredaran darah di kaki (*claudication*) atau jika Anda mempunyai faktor resiko untuk penyakit kardiovaskular seperti tekanan darah tinggi (hipertensi), diabetes, atau masalah pada kadar lemak darah Anda (gangguan lipid).
- Jika Anda memiliki **gangguan jantung** atau gangguan ritme jantung, seperti detak jantung yang tidak teratur atau sinyal elektrik yang abnormal yang disebut "*prolongation of the QT interval"* atau interval QT yang diperpanjang.
- Jika Anda sedang mendapatkan pengobatan dengan obat-obatan yang mempengaruhi detak jantung (antiaritmia) atau obat-obatan yang mungkin mempunyai efek yang tidak diinginkan terhadap fungsi jantung (Obat-obatan yang memperpanjang interval QT) (lihat pada bagian "Mengkonsumsi obat lain dengan TASIGNA").
- Jika Anda mengalami gangguan hati atau sedang mendapatkan pengobatan dengan obat-obatan yang mempengaruhi hati (lihat pada bagian "Mengkonsumsi obat lain dengan TASIGNA").
- Jika Anda mengalami kekurangan kalium atau magnesium.
- Jika Anda pernah mengalami pankreatitis (peradangan pada pankreas).
- Jika Anda pernah mengalami operasi yang melibatkan penghilangan seluruh bagian perut (gastrektomi total).
- Jika Anda pernah memiliki gejala seperti mudah memar, merasa lelah atau nafas pendek, atau pernah mengalami infeksi berulang.
- Jika Anda pernah atau sedang mengalami infeksi hepatitis B. Selama pengobatan dengan TASIGNA, hepatitis B dapat aktif kembali. Dokter Anda akan mengecek terhadap gejala infeksi hepatitis B sebelum Anda memulai pengobatan dengan TASIGNA.

Hubungi dokter Anda, jika ada kondisi diatas yang berlaku untuk Anda.

Pemantauan selama pengobatan dengan TASIGNA

Segera hubungi dokter Anda atau secepat mungkin jika Anda pingsan (hilang kesadaran) atau mengalami detak jantung yang tidak teratur selama mengkonsumsi TASIGNA karena hal ini mungkin saja disebabkan oleh kondisi jantung yang serius. Kasus yang tidak umum (antara 1 sampai 1.000 dan kurang dari 1 pada setiap 100 pasien) dari kematian mendadak telah dilaporkan pada pasien yang menerima TASIGNA. Perpanjangan interval QT atau detak jantung yang tidak teratur dapat mengakibatkan kematian mendadak.

Segera hubungi dokter Anda atau secepat mungkin jika Anda mengalami nyeri dada atau perasaan tidak nyaman, gejala nerologis yang permanen atau dapat kembali normal seperti mati rasa atau kelemahan atau masalah pada gerakan atau saat berbicara, atau nyeri, mati rasa, perubahan warna atau perasaan dingin pada tungkai (lengan atau kaki). Kejadian kardiovaskular serius (antara 1 sampai 6 dalam 100 pasien setelah 5 tahun dari tindak lanjut) termasuk masalah

pada peredaran darah di kaki (penyakit oklusif arteri perifer), penyakit hati iskemik, dan masalah pada peredaran darah di otak (penyakit serebrovaskular iskemik) telah dilaporkan pada pasien yang mengkonsumsi TASIGNA. Direkomendasikan untuk melakukan penilaian terhadap lemak darah dan gula darah sebelum memulai pengobatan dengan TASIGNA dan memonitor selama pengobatan.

Segera hubungi dokter Anda atau secepat mungkin jika Anda mengalami deman, ruam pada kulit, nyeri sendi dan peradangan juga kelelahan, hilang nafsu makan, mual, *jaundice* (kulit kekuningan), nyeri pada perut bagian kanan atas, warna pucat pada feses dan warna gelap pada urin (hal ini merupakan tanda-tanda reaktivasi virus hepatitis B).

Mengkonsumsi obat lain dengan TASIGNA

TASIGNA dapat mengganggu kerja obat-obatan lain.

Mohon beritahukan dokter atau apoteker Anda jika Anda sedang atau baru saja mengkonsumsi obat-obatan lain, termasuk obat-obatan yang bisa didapat tanpa resep dokter.

Termasuk jika Anda sedang mengkonsumsi obat-obatan di bawah ini:

- Obat antiaritmia seperti amiodarone, disopyramide, procainamide, quinidine, sotalol – obat-obatan ini digunakan untuk mengobati denyut jantung yang tidak teratur.
- Klorokuin, halofantrin, klaritromisin, haloperidol, methadol, moksifloksasin, bepridil, pimozide – obat-obatan ini dapat menimbulkan efek yang tidak diinginkan terhadap fungsi hati (perpanjangan QT).
- Ketokonazole, itraconazole, voriconazole, chlarithromycin, telithromycin – obat-obatan ini digunakan untuk mengobati infeksi.
- Ritonavir – obat anti HIV yang termasuk ke dalam kelas obat-obatan anti-protease.
- Carbamazepine, fenobarbital, fenitoin – obat-obatan ini digunakan untuk mengobati epilepsi.
- Rifampisin – digunakan untuk mengobati tuberkulosis.
- *St. John's Wort* – produk herbal yang digunakan untuk mengobati depresi dan kondisi lain (juga dikenal sebagai *Hypericum Perforatum*).
- Midazolam – digunakan untuk mengurangi kecemasan sebelum operasi.
- Alfentanil dan fentanil – digunakan untuk mengobati rasa nyeri dan digunakan sebagai obat penenang sebelum dan selama operasi atau prosedur medis.
- Siklosporin, sirolimus dan takrolimus – obat-obatan yang digunakan untuk menekan kemampuan tubuh untuk membela diri untuk melawan infeksi; biasanya digunakan untuk mencegah penolakan organ transpan seperti hati, jantung dan ginjal.
- Dihidroergotamin dan ergotamin – digunakan untuk mengobati demensia dan migrain.
- Lovastatin, simvastatin – digunakan untuk mengobati kadar lemak tinggi dalam darah.
- Warfarin – digunakan untuk mengobati gangguan pembekuan darah.
- Astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil atau ergot alkaloid (ergotamine, dihydroergotamine).

Obat-obatan diatas harus dihindari selama pengobatan dengan TASIGNA. Jika Anda sedang mengkonsumsi obat-obatan tersebut, dokter Anda mungkin akan meresepkan obat alternatif lain.

Sebagai tambahan, beritahukan kepada dokter atau apoteker Anda, jika Anda sedang mengkonsumsi antasida (obat maag). Obat-obatan di bawah ini perlu dikonsumsi secara terpisah dengan TASIGNA:

- Antasida yang disebut sebagai penghambat H2 (H2 *blockers*) dapat menurunkan produksi asam dalam lambung – obat-obatan ini harus diminum 10 jam sebelum atau 2 jam sesudah mengkonsumsi TASIGNA.
- Antasida yang mengandung aluminium hidroksida, magnesium hidroksida dan simetikon berfungsi menurunkan tingkat keasaman yang tinggi dalam lambung – obat-obatan ini harus diminum 2 jam sebelum atau 2 jam sesudah mengkonsumsi TASIGNA.

Beritahukan dokter Anda jika Anda sedang mengkonsumsi TASIGNA dan Anda diresepkan obat baru, termasuk obat-obatan yang didapat tanpa resep dokter, yang belum pernah Anda konsumsi sebelumnya selama pengobatan dengan TASIGNA.

Penggunaan TASIGNA bersama makanan dan minuman

- **TASIGNA tidak boleh dikonsumsi bersama makanan.** Kapsul TASIGNA dikonsumsi sedikitnya 2 jam sebelum makan dan kemudian tunggu setidaknya 1 jam sebelum Anda makan kembali. Untuk informasi lebih lanjut, lihat bagian “Kapan mengkonsumsi TASIGNA” pada brosur ini. Konsumsi TASIGNA bersamaan dengan makanan dapat meningkatkan kadar TASIGNA di dalam darah, dan mungkin bisa membahayakan.
- **Jangan memakan atau meminum produk atau jus yang mengandung *grapefruit*, belimbing, buah delima, jeruk *Seville* dan buah-buahan sejenis selama pengobatan.** Hal ini dapat meningkatkan kadar TASIGNA di dalam darah, dan mungkin bisa membahayakan. Jika Anda ragu, hubungi dokter atau apoteker Anda.
- **Jika Anda tidak mampu menelan kapsul,** Anda dapat mencampur isi kapsul ke dalam 1 sendok teh saus apel (*pureed apple*) dan segera telan campuran tersebut. Untuk informasi lebih lanjut, lihat bagian “Bagaimana cara mengkonsumsi TASIGNA”.

Pasien usia lanjut (usia 65 tahun keatas)

TASIGNA dapat dikonsumsi oleh pasien berusia 65 tahun ke atas dengan dosis yang sama dengan pasien dewasa.

Pasien anak-anak dan remaja (di bawah 18 tahun)

Belum ada pengalaman terkait penggunaan TASIGNA pada pasien anak-anak dan remaja.

Kehamilan dan Menyusui

TASIGNA tidak dianjurkan untuk digunakan selama kehamilan kecuali benar-benar diperlukan. Jika Anda sedang hamil atau berpikir bahwa Anda sedang hamil, beritahukan kepada dokter Anda yang akan mendiskusikan dengan Anda apakah Anda dapat mengkonsumsi TASIGNA selama kehamilan.

Anda tidak boleh mengkonsumsi TASIGNA jika Anda sedang menyusui dan selama dua minggu setelah dosis terakhir karena dapat membahayakan bayi Anda. Beritahukan kepada dokter Anda jika Anda sedang menyusui.

Wanita yang berpotensi untuk hamil

Wanita yang berpotensi untuk hamil harus menggunakan kontrasepsi yang efektif selama mengkonsumsi TASIGNA dan selama 2 minggu setelah selesai pengobatan.

Tanyakan kepada dokter atau apoteker Anda untuk saran sebelum Anda mengkonsumsi obat apapun.

Mengemudi dan menjalankan mesin

Jika Anda mengalami efek samping (seperti pusing atau gangguan penglihatan) yang mungkin berpengaruh terhadap kemampuan untuk mengemudi atau menggunakan peralatan dan mengoperasikan mesin setelah menggunakan TASIGNA, Anda harus menghindari aktifitas tersebut hingga efek samping yang Anda alami menghilang.

Informasi penting terkait kandungan lain dari TASIGNA

TASIGNA mengandung laktosa (gula susu). Beritahukan dokter Anda sebelum Anda mengkonsumsi TASIGNA, jika Anda memiliki intoleransi terhadap laktosa.

3. Bagaimana cara mengkonsumsi TASIGNA

Ikuti instruksi yang diberikan oleh dokter Anda secara seksama. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak TASIGNA yang dikonsumsi

Pasien dewasa yang baru terdiagnosa CML: dosis yang direkomendasikan adalah 2 kapsul TASIGNA 150 mg diminum dua kali sehari (300 mg dua kali sehari).

Dokter Anda mungkin meresepkan dosis yang lebih rendah tergantung respon Anda terhadap pengobatan.

Kapan mengkonsumsi TASIGNA

Kapsul TASIGNA dikonsumsi:

- Sebanyak dua kali sehari (kira-kira setiap 12 jam)
- Setidaknya 2 jam sebelum makan makanan apapun
- Kemudian tunggu sampai sekurangnya 1 jam sebelum Anda makan kembali

Jika Anda memiliki pertanyaan mengenai kapan mengkonsumsi TASIGNA, hubungi dokter atau apoteker Anda.

Mengkonsumsi TASIGNA pada waktu yang sama setiap hari akan membantu Anda mengingat kapan mengkonsumsi TASIGNA.

Bagaimana cara mengkonsumsi TASIGNA

- Telan kapsul secara utuh dengan air.

  Jangan membuka kapsul.

  Jangan mengkonsumsi makanan apapun bersamaan dengan kapsul.
- **Jika Anda tidak mampu menelan kapsul:**
  - **Buka** kapsul.
  - **Campur** isi kapsul dalam 1 sendok teh saus apel (*pureed apple*).
    - Gunakan hanya **satu sendok teh** saus apel (tidak boleh lebih).
    - Gunakan **hanya saus apel** untuk campuran (tidak boleh makanan lain).
  - Telan campuran sesegera mungkin.

Berapa lama pengobatan dengan TASIGNA

Teruskan pengobatan dengan TASIGNA setiap hari selama dianjurkan oleh dokter Anda. Pengobatan ini merupakan pengobatan jangka panjang. Dokter Anda akan memantau secara rutin kondisi Anda untuk mengecek bahwa pengobatan yang dilakukan sesuai dengan efek yang diharapkan.

Dokter Anda mungkin dapat mempertimbangkan untuk menghentikan pengobatan dengan TASIGNA berdasarkan kriteria tertentu.

Penghentian TASIGNA tanpa persetujuan dokter Anda berisiko buruk terhadap penyakit Anda yang dapat mengancam jiwa. Jika Anda memiliki pertanyaan terkait berapa lama pengobatan dengan TASIGNA, hubungi dokter atau apoteker Anda.

Apabila Anda mengkonsumsi TASIGNA lebih dari yang seharusnya

Apabila Anda mengkonsumsi TASIGNA lebih dari yang seharusnya, atau ada orang lain yang tidak sengaja meminum obat anda, segera hubungi dokter Anda atau Rumah Sakit terdekat untuk penanganan segera. Tunjukanlah kemasan obat tersebut jika memungkinkan. Penanganan medis mungkin diperlukan.

Apabila Anda lupa mengkonsumsi TASIGNA

Jangan mengkonsumsi dosis ganda untuk menutupi dosis yang telah Anda lewatkan. Minumlah dosis selanjutnya sesuai jadwal pengobatan Anda

Apabila Anda menghentikan pengobatan dengan TASIGNA

Jangan menghentikan pengobatan dengan TASIGNA kecuali atas anjuran dokter. Jika Anda memiliki pertanyaan lebih lanjut mengenai obat ini, hubungi dokter atau Apoteker Anda.

Apabila dokter Anda menganjurkan penghentian pengobatan dengan TASIGNA

Dokter Anda akan mengevaluasi pengobatan Anda secara rutin dengan tes diagnosis yang spesifik dan memutuskan apakah Anda perlu meneruskan pengobatan dengan TASIGNA. Jika Anda dianjurkan untuk menghentikan pengobatan dengan TASIGNA, dokter Anda akan meneruskan untuk memantau CML Anda sebelum, selama dan setelah Anda menghentikan pengobatan dengan TASIGNA dan Anda juga dapat dianjurkan untuk memulai kembali pengobatan dengan TASIGNA jika diperlukan.

4. Efek samping yang mungkin terjadi

Seperti obat-obatan lainnya, pasien yang diobati dengan TASIGNA mungkin mengalami efek samping, meskipun tidak semua pasien mengalaminya. Kebanyakan efek samping yang terjadi adalah efek samping ringan sampai sedang dan akan hilang setelah beberapa hari atau beberapa minggu pengobatan.

Tidak perlu khawatir dengan kemungkinan efek samping yang tertera di bawah ini. Anda belum tentu akan mengalaminya.

Beberapa efek samping yang mungkin serius

Segera hubungi dokter Anda jika Anda pingsan (mengalami kehilangan kesadaran) atau mengalami detak jantung yang tidak teratur ketika mengkonsumsi TASIGNA, hal ini mungkin diakibatkan oleh kondisi jantung yang serius.

Beberapa efek samping, terutama jika terjadi bersamaan dengan efek samping lain, mungkin menunjukan kondisi serius seperti tersebut di bawah ini. Efek samping berikut bisa terjadi sangat umum, umum, dan tidak umum atau bahkan dilaporkan hanya pada sedikit pasien.

- Nyeri dada atau perasaan tidak nyaman, tekanan darah tinggi atau rendah, detak jantung yang tidak teratur (cepat atau lambat), jantung berdebar, pingsan, bibir, gusi atau kulit berwarna kebiruan (hal ini merupakan tanda-tanda gangguan pada jantung).
- Kenaikan berat badan yang cepat, pembengkakan pada tangan, pergelangan, kaki atau wajah (hal ini merupakan tanda-tanda retensi cairan).
- Kesulitan atau sakit pada saat bernafas, batuk, mengi dengan atau tanpa demam (hal ini merupakan tanda-tanda kelainan pada paru-paru).
- Demam, mudah lebam atau pendarahan yang tidak dapat dijelaskan, infeksi berat atau sering terjadi infeksi, kelelahan yang tidak dapat dijelaskan (hal ini merupakan tanda-tanda kelainan pada darah).
- Kelemahan atau kelumpuhan di anggota badan atau muka, kesulitan berbicara, sakit kepala yang berat, melihat, merasakan atau mendengar sesuatu yang tidak ada, perubahan penglihatan, kehilangan kesadaran, linglung, disorientasi, gemetar, kesemutan, nyeri atau mati rasa pada jari-jari tangan dan kaki (hal ini merupakan tanda-tanda gangguan sistem saraf).
- Rasa haus, kulit kering, mudah iritasi, urin berwarna gelap, penurunan jumlah urin, kesulitan atau rasa nyeri saat berkemih, sering merasakan ingin berkemih, adanya darah dalam urin, perubahan warna urin yang tidak normal (hal ini merupakan tanda-tanda ganguan pada ginjal atau saluran kemih).
- Gangguan penglihatan termasuk penglihatan kabur, penglihatan ganda atau kilatan cahaya yang dirasakan, penurunan ketajaman atau kehilangan penglihatan, darah pada mata, peningkatan sensitifitas mata terhadap cahaya, sakit mata, kemerahan pada mata, mata gatal, atau iritasi mata, mata kering, bengkak atau gatal pada kelopak mata (hal ini merupakan tanda-tanda gangguan pada mata).
- Pembengkakan atau nyeri pada salah satu bagian tubuh (hal ini merupakan tanda-tanda pembekuan pembuluh darah).
- Nyeri pada perut, mual, muntah darah, feses berwarna gelap atau berdarah, sembelit, *heartburn*, reflux asam lambung, pembengkakan atau perut kembung (hal ini merupakan tanda-tanda gangguan saluran pencernaan).
- Nyeri yang parah pada perut bagian atas (tengah atau kiri) (mungkin merupakan tanda-tanda pembengkakan pankreas).
- Kulit dan mata berwarna kekuningan, mual, kehilangan nafsu makan, urin berwarna gelap (hal ini merupakan tanda-tanda gangguan hati).
- Benjolan merah yang terasa sakit, kulit memerah, pengelupasan, lepuhan pada kulit atau nyeri (hal ini merupakan tanda-tanda gangguan kulit).
- Nyeri pada sendi dan otot (hal ini merupakan tanda-tanda nyeri muskuloskeletal).
- Rasa haus yang berlebihan, peningkatan jumlah urin, peningkatan nafsu makan yang disertai dengan penurunan berat badan, kelelahan (hal ini merupakan tanda-tanda tingginya kadar gula dalam darah).

- Detak jantung cepat, mata melotot, penurunan berat badan, pembengkakan pada leher bagian depan (hal ini merupakan tanda-tanda kelenjar tiroid yang terlalu aktif)
- Peningkatan berat badan, kelelahan, rambut rontok, kelemahan otot, sering merasa kedinginan (hal ini merupakan tanda-tanda kelenjar tiroid yang kurang aktif).
- Sakit kepala berat yang sering diikuti dengan mual, muntah dan sensitifitas terhadap cahaya (hal ini merupakan tanda-tanda migrain).
- Pusing, sensasi seperti berputar (hal ini merupakan tanda-tanda vertigo).
- Mual, nafas pendek, detak jantung tidak teratur, kekeruhan urin, kelelahan dan/atau rasa tidak nyaman pada sendi yang berhubungan dengan hasil lab yang abnormal (misalnya tingginya kadar kalium, asam urat dan fosfor dalam darah serta rendahnya kadar kalsium dalam darah).
- Rasa nyeri atau tidak nyaman, lemah atau kram pada otot kaki yang mungkin terjadi akibat penurunan aliran darah, borok atau bekas luka yang lama sembuh atau tidak sembuh-sembuh dan dapat terjadi perubahan warna pada luka (seperti bertambah biru atau pucat) atau perubahan suhu pada luka (lebih dingin). Hal ini merupakan tanda-tanda adanya penghambatan arteri pada bagian tubuh yang terdampak (misal kaki, tangan atau jari).
- Reaktivasi kembali dari infeksi hepatitis B jika Anda sebelumnya pernah terinfeksi hepatitis B (sejenis infeksi hati).

Jika Anda mengalami gejala-gejala diatas, **segera hubungi dokter Anda.**

Efek samping lain yang mungkin terjadi

Efek samping lainnya termasuk yang tercantum di bawah ini. Jika efek samping ini menjadi parah, beritahukan dokter, apoteker atau tenaga profesional kesehatan Anda.

Berikut ini adalah sebagian efek samping yang sangat umum: dapat mempengaruhi lebih dari 1 dari 10 orang

- Sakit perut, mual, muntah
- Sembelit, diare
- Sakit kepala
- Kelelahan/kurang tenaga
- Nyeri otot dan sendi
- Ruam, kulit kering, dan gatal
- Rambut rontok
- Nyeri muskuloskeletal, nyeri otot, nyeri pada tangan dan kaki, nyeri pada sendi, nyeri pada tulang dan nyeri pada tulang belakang setelah menghentikan pengobatan dengan TASIGNA.

- Tingkat bilirubin dalam darah tinggi (fungsi liver)
- Tingkat lipase dalam darah tinggi (fungsi pankreas)

Jika efek samping diatas berpengaruh berat pada Anda, **segera hubungi dokter Anda.**

Berikut ini adalah sebagian efek samping yang umum: dapat mempengaruhi hingga 1 dari setiap 10 orang

- Infeksi saluran pernafasan bagian atas.
- Perut terasa tidak nyaman setelah makan, perut kembung
- Nyeri tulang, kejang otot
- Rasa nyeri termasuk nyeri pada punggung, leher, tangan dan kaki atau rasa tidak nyaman pada salah satu bagian tubuh.
- Jerawat, kutil, penurunan sensitifitas kulit, gatal-gatal, keringat berlebihan pada malam hari.
- Pengingkatan atau penurunan berat badan, penurunan nafsu makan, gangguan pada indera pengecap
- Susah tidur, depresi, kecemasan
- Gangguan suara
- Mimisan
- Sering berkemih
- Perasaan tidak enak badan

Jika efek samping diatas berpengaruh berat pada Anda, **segera hubungi dokter Anda.**

Berikut ini adalah sebagian efek samping yang jarang: dapat mempengaruhi hingga 1 dari setiap 100 orang

- Mulut kering dan pecah-pecah
- Nyeri pada payudara
- Encok
- Peningkatan nafsu makan
- Kurang perhatian
- Gangguan ereksi, pembesaran payudara pada pria
- Gejala flu
- Radang tenggorokan
- Pneumonia, bronkitis, infeksi saluran kemih, sariawan pada mulut atau vagina, infeksi virus herpes

- Kekakuan pada otot dan sendi, pembengkakan sendi
- Perubahan suhu tubuh (termasuk merasa kepanasan atau kedinginan)
- Gigi sensitif

Jika efek samping diatas berpengaruh berat pada Anda, **segera hubungi dokter Anda.**

Efek samping di bawah ini telah dilaporkan pada sangat sedikit pasien yang diobati dengan TASIGNA

- Alergi (hipersensitivitas) terhadap TASIGNA
- *Hand-foot syndrome* (kemerahan dan/atau pembengkakan dan mungkin pengelupasan pada telapak tangan dan kaki), *psoriasis* (bercak tebal berwarna merah atau keperakan pada kulit, peningkatan sensitifitas kulit terhadap cahaya, infeksi jamur pada kaki, kista kulit, perubahan warna kulit, penipisan atau penebalan kulit dan penebalan lapisan terluar kulit).
- Kesulitan mendengar, nyeri pada telinga, bunyi mendering pada telinga
- Nyeri sendi
- Gangguan suasana hati, hilang ingatan
- Warna urin yang abnorma
- *Enterocolitis* (radang usus)
- Wasir *(haemorrhoids),* abses anal
- Perasaan mengeras pada payudara, pembengkakan puting, periode yang berat
- Pendarahan, nyeri, pembesaran gusi, kutil mulut
- Keinginan untuk menggerakan salah satu bagian tubuh (umumnya kaki) untuk mengatasi rasa tidak nyaman.
- Kelumpuhan otot wajah

Jika efek samping diatas berpengaruh berat pada Anda, **segera hubungi dokter Anda.**

Selama pengobatan dengan TASIGNA, Anda mungkin akan mengalami hasil tes darah yang abnormal seperti:

- Kadar sel darah yang rendah (sel darah putih, sel darah merah, platelet) atau hemoglobin.
- Peningkatan jumlah trombosit atau sel darah putih, atau jenis sel darah putih tertentu (eosinofil) dalam darah.
- Kadar bilirubin atau enzim hati yang tinggi (yang terkait dengan fungsi hati).
- Kadar lipase atau amilase dalam darah yang tinggi (yang terkait dengan fungsi pankreas).

- Kadar enzim lainnya dalam darah yang tinggi (fosfatase alkali, laktat dehidrogenase atau kreatin fosfokinase).
- Kadar kreatinin atau urea dalam darah yang tinggi (yang terkait dengan fungsi ginjal).
- Kadar gula darah yang tinggi atau rendah.
- Kadar lemak dalam darah yang tinggi (termasuk kolesterol).
- Kadar kalium, kalsium, fosfor atau asam urat dalam darah yang tinggi.
- Kadar magnesium, kalium, natrium, kalsium, atau fosfor dalam darah yang rendah.
- Perubahan protein dalam darah (kadar globulin atau paraprotein yang rendah).
- Kadar hormon paratiroid yang tinggi (hormon yang mengatur tingkat kalsium dan fosfor), tingkat insulin tinggi atau rendah (hormon yang mengatur kadar gula darah).

Jika efek samping diatas mempengaruhi Anda, **ikuti anjuran dari dokter Anda.**

Jika Anda mengalami efek samping yang tidak tercantum dalam brosur ini, hubungi dokter atau apoteker Anda.

5. Cara Penyimpanan TASIGNA

- Jangan gunakan TASIGNA setelah tanggal kadaluwarsa yang tercantum pada kemasan.
- Simpan pada suhu di bawah 30°C.
- Simpan pada kemasan aslinya untuk melindungi dari kelembaban.
- Jangan digunakan jika kemasan rusak atau ada tanda-tanda kerusakan.
- Jauhkan dari jangkauan dan penglihatan anak-anak.
- Jangan buang obat ke dalam pembuangan limbah rumah tangga. Tanyakan Apoteker Anda bagaimana membuang obat yang sudah lama tidak gunakan. Hal ini akan membantu perlindungan lingkungan.

6. Informasi lebih lanjut

Kandungan TASIGNA

Zat aktif TASIGNA adalah nilotinib. Tiap kapsul 150 mg mengandung 150 mg nilotinib.

Kandungan lainnya adalah:

- Laktosa monohidrat, *crospovidone*, *poloxamer 188*, silika koloidal, silikon dioksida koloidal/anhidrat, dan magnesium stearat.
- Cangkang kapsul TASIGNA mengandung gelatin, titanium dioksida (E171), *iron oxide yellow* (E172), *iron oxide red* (E172), dan *iron oxide black* (E172) untuk pencetakan.

Bagaimana bentuk TASIGNA

TASIGNA 150 mg berbentuk kapsul berwarna merah. Terdapat tulisan berwarna hitam NVR/BCR yang dicetak pada setiap kapsul.

Kemasan

TASIGNA kapsul 150 mg: Dus, 7 blister @ 4 kapsul Reg.No. DKIXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Pemegang Ijin Edar

PT. Novartis Indonesia

Pabrik Pembuat

Dibuat oleh Novartis Pharma Stein AG, Stein, Swiss untuk Novartis Pharma AG, Basel, Swiss

Dikemas dan dirilis oleh Lek d.d., PE PROIZVODNJA LENDAVA, Lendava, Slovenia.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Apabila Anda memiliki pertanyaan mengenai obat ini, mohon hubungi dokter, apoteker atau tenaga profesional kesehatan Anda.

PIL based on BPL 2.2 18-May-2020 and PP site transfer to Lek Lendava

TASIGNA®

(nilotinib)

150 mg hard capsules

Leaflet

EREG100005VR12000251

Tradename

150 mg hard capsules

TASIGNA® 150 mg hard capsules

Description and composition

Pharmaceutical form

Hard capsules

150 mg hard capsules

White to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint "NVR/BCR".

Active substance

150 mg hard capsules

Each capsule contains 150 mg nilotinib base (as hydrochloride, monohydrate).

Excipients

150 mg hard capsules

Capsule content: Lactose monohydrate, Crospovidone, Poloxamer 188, Silica colloidal, anhydrous/Colloidal silicon dioxide, Magnesium stearate.

Capsule shell: Gelatin; Titanium dioxide (E 171); Iron oxide, red (E 172), Iron oxide, yellow (E 172).

Printing ink: Iron oxide, black (E 172).

Indications

TASIGNA hard capsule is indicated for the:

- treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Patients who have been treated with TASIGNA for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections Dosage regimen and administration and Clinical studies).

Dosage regimen and administration

Therapy with TASIGNA should be initiated by a physician experienced in the treatment of patients with CML.

TASIGNA may be given in combination with haematopoietic growth factors such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) if clinically indicated. TASIGNA may be given with hydroxyurea or anagrelide if clinically indicated.

Monitoring of response to TASIGNA therapy in Ph+ CML patients should be performed both 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.

General target population

Dosage in adult patients with newly diagnosed Ph+ CML-Chronic Phase (CP)

The recommended dose of TASIGNA is 300 mg twice daily (see section Clinical studies). Treatment should be continued as long as the patient continues to benefit.

Dosage in newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response (MR 4.5)

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with TASIGNA at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of TASIGNA should be initiated by a physician experienced in the treatment of patients with CML (see sections Warnings and precautions and Clinical studies).

Patients who are eligible to discontinue TASIGNA therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least molecular response 4.5 (MR4.5).

Patients who lose major molecular response must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. TASIGNA therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate TASIGNA therapy should have their BCR-ABL transcript levels monitored monthly until major molecular response is re-established (see sections Warnings and precautions and Clinical studies).

Monitoring recommendations and dose adjustments

A baseline electrocardiogram (ECG) is recommended prior to initiating therapy with TASIGNA and should be repeated after 7 days and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to TASIGNA administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see section Warnings and precautions).

Increases in total serum cholesterol levels have been reported with TASIGNA therapy (see section Warnings and precautions). Lipid profiles should be determined prior to initiating

TASIGNA therapy, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with TASIGNA therapy (see section Warnings and precautions). Blood glucose levels should be assessed prior to initiating TASIGNA therapy and monitored during treatment.

Due to possible occurrence of Tumor Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with TASIGNA (see section Adverse drug reactions).

TASIGNA may need to be temporarily withheld and/or dose reduced for haematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukaemia (see Table-1).

Table-1 Dose adjusments for neutropenia and thrombocytopenia

Newly diagnosed CML in chronic phase at 300 mg twice daily	ANC* <1 x 10^9/L and/or platelet counts <50 x 10^9/L	1. Stop TASIGNA, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and/or platelets >50 x 10^9/L 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required

**ANC = absolute neutrophil count*

If clinically significant moderate or severe non-haematologic toxicity develops, dosing should be interrupted, and may be resumed at 400 mg once daily once the toxicity has resolved. If clinically appropriate, re-escalation of the dose to 300 mg twice daily should be attempted.

Elevated serum lipase: For Grade 3 to 4 lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated (see sections Warnings and precautions for use and Adverse drug reactions).

Elevated bilirubin and hepatic transaminases: For Grade 3 to 4 bilirubin or hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see section Adverse drug reactions).

Special populations

Renal impairment

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

Hepatic impairment

TASIGNA has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST >2.5 (or >5, if related to disease) times the

upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic.

Cardiac disorders

In clinical studies, patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia were excluded.

Caution should be exercised in patients with relevant cardiac disorders (see section Warnings and precautions).

Pediatric patients (below 18 years)

Clinical studies have not been conducted in children and adolescents.

Geriatrics patients (65 years of age or above)

Approximately 12% of subjects in the clinical studies (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP) were 65 years of age or older. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults 18 to 65 years of age.

Method of administration

TASIGNA should be taken twice daily, at approximately 12 hour intervals, and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see section Warnings and precautions).

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used (see sections Clinical pharmacology).

If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose.

Contraindications

TASIGNA is contraindicated in patients with known hypersensitivity to nilotinib or to any of the excipients.

Warnings and precautions

Myelosuppression

Treatment with TASIGNA is often associated with thrombocytopenia, neutropenia and anaemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and in particular in patients with CML-AP. Complete blood

counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or reducing the dose (see section Dosage regimen and administration).

QT Prolongation

In vitro data suggest that nilotinib has the potential to prolong cardiac ventricular repolarization (QT interval).

In the Phase III study in newly diagnosed Ph+ CML-CP patients the change from baseline in mean time-averaged QTcF interval at steady-state observed in the nilotinib 300 mg twice daily group was 6 msec. At the recommended dose of 300 mg twice daily no patient had an absolute QTcF of >480 msec and no events of Torsades de Pointes were observed.

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF>450 msec. In addition, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of torsades de pointes (either transient or sustained) were observed.

Clinically meaningful prolongation of the QT interval may occur when TASIGNA is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT interval; therefore, concomitant administration should be avoided (see section Warnings and precautions: Food-effects and section Interactions).

The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation (see section Dosage regimen and administration).

TASIGNA should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with long QT syndrome,
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

Sudden death

In clinical trials, uncommon cases (0.1 to 1%) of sudden death have been reported in patients in imatinib-resistant or -intolerant CML patients in chronic and accelerated phase receiving TASIGNA with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study.

Cardiovascular events

Cardiovascular events were reported in a randomized, Phase III nilotinib trial in newly diagnosed CML patients and observed in the post-marketing reports. With a median time on

therapy of 60.5 months in the clinical trial, Grade 3/4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg twice a day respectively), ischemic heart disease (2.2% and 6.1% at 300 mg and 400 mg twice a day respectively) and ischemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg twice a day respectively). If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during TASIGNA therapy according to standard guidelines (see section Dosage regimen and administration).

Fluid retention

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary edema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the etiology should be evaluated and patients treated accordingly (see section Dosage regimen and administration).

Hepatitis B reactivation

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as nilotinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section Adverse drug reactions).

Patients should be tested for hepatitis B infection before initiating treatment with nilotinib. Patients currently on nilotinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

Special monitoring of Ph+ CML-CP patients who have achieved a sustained deep molecular response

Eligibility for discontinuation of treatment

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCR-ABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after TASIGNA treatment discontinuation.

Monitoring of patients who have discontinued therapy

Monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation (see sections Dosage regimen and administration and Clinical studies).

Loss of Major Molecular Response (MMR) or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Frequent monitoring of BCR-ABL transcript levels and complete blood count with differential is required to detect possible loss of remission (see sections Dosage regimen and administration and Clinical studies).

Laboratory tests and monitoring

Blood lipids

In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice a day, had a Grade 3/4 elevation in total cholesterol; however, there were no Grade 3/4 elevations in the 300 mg twice a day dose group (see section Adverse drug reactions). It is recommended that the lipid profiles be determined before initiating treatment with TASIGNA, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy (see section Dosage regimen and administration). If a hydroxymethylglutaryl-CoA (HMG CoA) reductase inhibitor (a lipid lowering agent) is needed, please refer to section Interactions, before starting treatment since certain HMG CoA reductase inhibitors are metabolized by the CYP3A4 pathway.

Blood glucose

In a Phase III study in newly diagnosed CML patients, 6.9% of the patients treated with 400 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose; and 7.2% of the patients treated with 300 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose. It is recommended that the glucose levels should be assessed before initiating treatment with Tasigna and monitored during treatment as clinically indicated (see section Dosage regimen and administration). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

Interactions

The administration of TASIGNA with agents that are strong CYP3A4 inhibitors and drugs that may prolong the QT interval such as anti-arrhythmic medicines should be avoided (see section Dosage regimen and administration and section Interactions). Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted if possible (see section Interactions). If transient interruption of treatment with TASIGNA is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see section Dosage regimen and administration, section Interactions and section Clinical pharmacology).

Concomitant use of TASIGNA with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving TASIGNA, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section Interactions).

Food-effects

The bioavailability of nilotinib is increased by food. TASIGNA must not be taken in conjunction with food (see section Dosage regimen and administration and section Interactions) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

Hepatic impairment

Tasigna has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with alanine transaminase (ALT) and/ or aspartate aminotransferase (AST) >2.5 (or >5, if related to disease) times the upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment (see section Dosage regimen and administration).

Serum lipase

Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered in order to exclude pancreatitis (see section Dosage regimen and administration).

Total gastrectomy

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section Clinical pharmacology). More frequent follow up of these patients should be considered.

Tumor lysis syndrome

Cases of TLS have been reported in patients treated with TASIGNA. For monitoring recommendations please refer to section Dosage regimen and administration.

Lactose

Since the capsules contain lactose, TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or of glucose-galactose malabsorption.

Interactions

Nilotinib is mainly metabolized in the liver with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-drug efflux pump, P-glycoprotein (Pgp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or Pgp.

Drugs that may increase nilotinib serum concentrations

In a Phase I study of nilotinib given in combination with imatinib (a substrate and moderator of P-gp and CYP3A4), both drugs had a slight inhibitory effect on CYP3A4 and/or PgP. When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%.

The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) (see section Dosage regimen and administration and Warnings and precautions regarding QT prolongation). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

Drugs that may decrease nilotinib serum concentrations

In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease plasma concentrations of nilotinib. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in C_{max} and 34% decrease in $AUC_{0-\infty}$). TASIGNA may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of TASIGNA was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of TASIGNA.

In the same study as above, administration of an antacid (aluminum hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of TASIGNA also did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of TASIGNA.

Drugs that may have their systemic concentration altered by nilotinib

In vitro nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 (Ki=0.13 microM). Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolized by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

In healthy subjects, nilotinib at clinically relevant concentrations was not found to alter the pharmacokinetics or pharmacodynamics of warfarin, a sensitive CYP2C9 substrate. TASIGNA can be used concurrently with warfarin without increasing the anticoagulant effect.

Anti-arrhythmic medicines and other drugs that may prolong the QT interval. Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil and pimozide) should be avoided (see section Warnings and precautions).

Food interactions

The absorption and the bioavailability of nilotinib is increased if it is taken with food, resulting in higher serum concentration (see section Dosage regimen and administration, Warnings and precautions and Clinical pharmacology).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk Summary

TASIGNA can cause fetal harm when administered to a pregnant woman. There are no adequate data on the use of TASIGNA in pregnant women. Reproductive studies in rats and rabbits have demonstrated that nilotinib induced embryo-toxicity and/or feto-toxicity (following prenatal exposure to nilotinib) at exposures equal to the one achieved in humans at the maximum recommended human dose of 400 mg twice daily. TASIGNA should not be used during pregnancy unless necessary. If the drug is used during pregnancy or if the patient becomes pregnant while taking TASIGNA, the patient must be informed of the potential risk to the fetus.

If a woman who is being treated with TASIGNA is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting TFR. If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate TASIGNA treatment during pregnancy (see sections Dosage regimen and administration and Warnings and precautions).

Animal Data

Nilotinib did not induce teratogenicity, but did show embryo- and feto-toxicity at doses which also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, with treatment of both males and females, and in the embryo-toxicity study with the treatment of females. Embryo-lethality and fetal effects (mainly decreased fetal weights, visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryo-toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels (NOAEL) was generally less or equal to that in humans at 800 mg/day.

In a pre- and postnatal study, the oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 postpartum resulted in maternal effects (reduced food consumption and lower body weight gains) and longer gestation period at 60 mg/kg. The maternal dose of 60 mg/kg was associated with decreased pup body weight and changes in some physical development parameters (the mean day for pinna unfolding, tooth eruption and eye opening was earlier). The NOAEL in maternal animals and offspring was a maternal dose of 20 mg/kg.

Lactation

Risk Summary

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that Nilotinib is excreted into breast milk. Lactating women should not breast-feed while taking TASIGNA and for 2 weeks after the last dose, as a risk to the infant cannot be excluded.

Females and males of reproductive potential

Contraception

Females

Females of reproductive potential must be advised to use effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving TASIGNA and for up to 2 weeks after ending treatment with TASIGNA.

Infertility

The effect of nilotinib on male and female fertility is not known. In animal studies no effects on sperm count/motility, and on fertility were noted in male and female rats up to the highest tested dose of approximately 5-fold greater than the recommended dosage for human.

Effects on ability to drive and use machines

No studies on the effects of nilotinib on the ability to drive and operate machines have been performed. Patients experiencing dizziness, visual impairment or other undesirable effects with a potential impact on the ability to safely drive or use machines should refrain from these activities as long as these undesirable effects persist (see section Adverse drug reactions).

Adverse drug reactions

Summary of the safety profile

The nilotinib safety profile described below is based on data from patients with newly diagnosed Ph+ CML-CP in a randomized, open label, active comparator-controlled Phase III trial (see Table 2 and section Indications).

In patients with newly diagnosed Ph+ CML-CP

The data reported below reflect exposure to TASIGNA from a randomized phase III study in patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment was 60.5 months (range 0.1 – 70.8 months).

Non-haematologic Adverse Drug Reactions (ADRs) reported with very common frequency (≥10%) were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia and upper abdominal pain. Most of these ADRs were mild to moderate in severity (Grade 1 or 2). Constipation, diarrhoea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema, vomiting and asthenia were observed less commonly (≤10% and >5%) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions, regardless of causality, occurred in 2% and <1% of patients, respectively, receiving TASIGNA 300 mg twice daily. Gastrointestinal hemorrhage, regardless of causality, was reported in 3% of these patients.

The change from baseline in mean time-averaged QTcF interval at steady state in the nilotinib recommended dose of 300 mg twice daily was 6 msec. In the nilotinib 400 mg twice daily group and the imatinib 400 mg once daily group the change from baseline in mean time-averaged QTcF interval at steady state was 6 msec and 3 msec respectively. No patient had an absolute QTcF of >500 msec in any of the TASIGNA treatment groups and no events of Torsades de Pointes were observed . QTcF increase from baseline that exceeds 60 msec was observed in 5 patients while on TASIGNA (one in the 300 mg twice daily treatment group and four in the 400 mg twice daily treatment group).

No patients in any treatment groups had a left ventricular ejection fraction (LVEF) <45% during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

No sudden deaths have been reported in any treatment group.

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (18%), neutropenia (15%), and anaemia (8%). Biochemistry ADRs include alanine aminotransferase increased (24%), hyperbilirubinemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycemia (4%), hypercholesterolemia (3%), and hypertriglyceridemia (<1%). See Table-4 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 10% of patients.

Most frequently reported adverse drug reactions

Non-haematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the patients in any of the TASIGNA clinical studies that served as a basis for the listed indications are shown in Table-2. These are ranked under heading of frequency, the most frequent first. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following (CIOMS III) convention: very common (≥1/10) or common (≥1/100 to <1/10). The frequency is based on the highest for any TASIGNA group in the two studies, using one decimal precision for percentages.

Table-2 Most frequently reported non-haematologic adverse drug reactions (≥5% in any TASIGNA Group)

			Newly diagnosed Ph+ CML-CP					
			60-month analysis					
			TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	Imatinib 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	Imatinib 400 mg once daily
			ALL GRADES (%)			GRADE 3 or 4 (%)		
System Organ Class	**Frequency**	**Adverse Drug Reaction**	**N=279 %**	**N=277 %**	**N=280 %**	**N=279 %**	**N=277 %**	**N=280 %**
Metabolism and nutrition disorders	Common	Decreased appetite[1]	4	4	3	0	0	0
Nervous system disorders	Very common	Headache	16	22	10	2	1	<1
Gastrointestinal disorders	Very common	Nausea	14	21	35	<1	1	<1
	Very common	Constipation	10	7	3	0	<1	0
	Very common	Diarrhoea	9	7	31	<1	0	3
	Very common	Vomiting	6	9	19	0	1	0
	Very common	Abdominal pain upper	10	9	8	1	0	<1
	Common	Abdominal pain	6	6	4	0	<1	0
	Common	Dyspepsia	5	5	6	0	<1	0
Skin and subcutaneous tissue disorders	Very common	Rash	33	39	14	<1	3	2
	Very common	Pruritus	18	16	5	<1	<1	0
	Very common	Alopecia	10	14	6	0	0	0
	Very Common	Dry Skin	10	12	5	0	0	0
	Common	Erythema	3	6	3	0	0	0

			Newly diagnosed Ph+ CML-CP					
			60-month analysis					
			TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	Imatinib 400 mg once daily	TASIGNA 300 mg twice daily	TASIGNA 400 mg twice daily	Imatinib 400 mg once daily
			ALL GRADES (%)			GRADE 3 or 4 (%)		
System Organ Class	**Frequency**	**Adverse Drug Reaction**	**N=279 %**	**N=277 %**	**N=280 %**	**N=279 %**	**N=277 %**	**N=280 %**
Musculoskeletal and connective tissue disorders	Very common	Myalgia	10	12	13	<1	<1	<1
	Very Common	Arthralgia	8	10	8	<1	0	<1
	Common	Muscle spasms	9	9	30	0	<1	1
	Common	Bone pain	4	5	4	0	<1	<1
	Common	Pain in extremity	5	3	8	<1	<1	<1
General disorders and administration site conditions	Very common	Fatigue	12	11	13	0	<1	1
	Common	Asthenia	9	5	9	<1	<1	0
	Common	Oedema peripheral	5	7	18	<1	0	0

[1] Also includes preferred term anorexia

Percentages are rounded to integer for presentation in this table. However, percentages with one decimal precision are used to identify terms with a frequency of at least 5% and to classify terms according to frequency categories

Additional data from clinical trials

The following adverse drug reactions were reported in patients in the TASIGNA clinical studies which serve as a basis for the listed indications at the recommended doses at a frequency of less than 5% (common is ≥1/100 to <1/10; uncommon is ≥1/1,000 to <1/100; single events are captured as frequency not known). For laboratory abnormalities, very common events (≥1/10) not included in Table-3 are also reported. These adverse reactions are included based on clinical relevance and ranked in decreasing order of seriousness within each category, obtained from two clinical studies: 1 Newly diagnosed Ph+ CML-CP 60 months' analysis and 2. Resistant or intolerant Ph+ CML-CP and CML-AP 24 months' analysis.

Table-3 Adverse drug reactions reported in clinical studies in adult patients

Infections and infestations	
Common:	Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Uncommon:	Pneumonia, bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
Neoplasms Benign, Malignant and Unspecified	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
Blood and lymphatic system disorders	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Not known:	Thrombocythaemia, leukocytosis
Immune system disorders	
Not known:	Hypersensitivity
Endocrine disorders	
Uncommon:	Hyperthyroidism, hypothyroidism
Not known:	Hyperparathyroidism secondary, thyroiditis
Metabolism and nutrition disorders	
Very common:	Hypophosphataemia (including blood phosphorus decreased)
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Uncommon:	Gout, dehydration, increased appetite, dyslipidaemia
Not known:	Hyperuricaemia, hypoglycaemia
Psychiatric disorders	
Common:	Depression, insomnia, anxiety
Not known:	Disorientation, confusional state, amnesia, dysphoria
Nervous system disorders	
Common:	Dizziness, peripheral neuropathy, hypoaesthesia, paraesthesia
Uncommon:	Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia
Not known:	Cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis,

	lethargy, dysaesthesia, restless legs syndrome
Eye disorders	
Common:	Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia)
Uncommon:	Vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation, conjunctival haemorrhage
Not known:	Papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease
Ear and labyrinth disorders	
Common:	Vertigo
Not known:	Hearing impaired, ear pain, tinnitus
Cardiac disorders	
Common:	Angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon:	Cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis
Not known:	Ventricular dysfunction, pericarditis, ejection fraction decrease
Vascular disorders	
Common:	Hypertension, flushing
Uncommon:	Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Not known:	Shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon:	Pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation
Not known:	Pulmonary hypertension, wheezing, oropharyngeal pain
Gastrointestinal disorders	
Common:	Pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Not known:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis
Hepatobiliary disorders	
Very Common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice
Not known:	Cholestasis, hepatomegaly
Skin and subcutaneous tissue disorders	
Common:	Night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform)
Uncommon:	Exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face
Not known:	Psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis
Musculoskeletal and connective tissue disorders	

	Common:	Musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness
	Uncommon:	Musculoskeletal stiffness, joint swelling
	Not known:	Arthritis
Renal and urinary disorders		
	Common:	Pollakiuria
	Uncommon:	Dysuria, micturition urgency, nocturia
	Not known:	Renal failure, hematuria, urinary incontinence, chromaturia
Reproductive system and breast disorders		
	Uncommon:	Breast pain, gynaecomastia, erectile dysfunction
	Not known:	Breast induration, menorrhagia, nipple swelling
General disorders and administration site conditions		
	Common:	Pyrexia, chest pain (including non-cardiac chest pain), pain, chest discomfort, malaise
	Uncommon:	Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
	Not known:	Localized oedema
Investigations		
	Very common:	Alanine aminotransferase increased, aspartate amino-transferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased
	Common:	Haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, blood insulin increased, weight decreased, weight increased, globulins decreased
	Uncommon:	Blood lactate dehydrogenase increased, blood urea increased
	Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

Laboratory abnormalities

Clinically relevant or severe abnormalities of routine haematologic or biochemistry laboratory values are presented in Table-4.

Table-4 Grade 3/4 Laboratory Abnormalities

	Newly diagnosed Ph+ CML-CP		
	TASIGNA 300 mg twice daily N = 279	**TASIGNA 400 mg twice daily N = 277**	**Imatinib 400 mg once daily N = 280**
Haematologic parameters			
Myelosuppression			
- Neutropenia	12%	11%	21%
- Thrombocytopenia	10%	12%	9%
- Anaemia	4%	5%	6%
Biochemistry parameters			
- Elevated creatinine	0%	0%	<1%
- Elevated lipase	9%	10%	4%
- Elevated SGOT (AST)	1%	3%	1%
- Elevated SGPT (ALT)	4%	9%	3%

- Hypophosphataemia	8%	10%	10%
	TASIGNA 300 mg twice daily N = 279	**TASIGNA 400 mg twice daily N = 277**	**Imatinib 400 mg once daily N = 280**
- Elevated Bilirubin (total)	4%	9%	<1%
- Elevated glucose	7%	7%	<1%
- Elevated Cholesterol (total)	0%	1%	0%
- Elevated tryiglycerides	0%	<1%	0%

Percentages with one decimal precision are used and rounded to integer for presentation in this table.

** parameter not collected*

Treatment discontinuation in Ph+ CML-CP patients who have achieved a sustained deep molecular response

After discontinuation of TASIGNA therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain.

In a Phase II clinical study with newly diagnosed patients with Ph+ CML-CP (N=190), musculoskeletal symptoms within a year of TASIGNA discontinuation were reported in 24.7% vs. 16.3% within the previous year on TASIGNA treatment.

In a Phase II clinical study with patients with Ph+ CML-CP on TASIGNA and previously treated with imatinib (N=126), musculoskeletal symptoms within a year of discontinuation were reported in 42.1% vs. 14.3% within the previous year on TASIGNA treatment.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experiences with Tasigna via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to nilotinib exposure.

Frequency not known: Tumor lysis syndrome, facial paralysis.

Overdosage

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents – Protein-tyrosine kinase inhibitor

ATC code: L01XE08.

Mechanism of action (MOA)

TASIGNA is a potent and selective inhibitor of the Abl tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukaemia cells. The drug binds strongly within the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in cell lines and in primary Philadelphia-chromosome positive leukaemia cells from CML patients. In murine models of CML, as a single agent nilotinib reduces tumour burden and prolongs survival following oral administration.

Pharmacodynamics (PD)

TASIGNA has little or no effect against the majority of other protein kinases examined, including SRC, except for the platelet-derived growth factor (PDGF), KIT, colony stimulating factor 1 receptor (CSF-1R), discoidin domain receptor (DDR) and Ephrin receptor kinases which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML (see Table-5).

Table-5 Kinase profile of nilotinib (phosphorylation IC_{50} nM)

BCR-ABL	PDGFR	KIT
20	69	210

Pharmacokinetics (PK)

Absorption

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, C_{max} and area under the concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively compared to fasting conditions when TASIGNA is given with food. Administration of TASIGNA 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see section Dosage regimen and administration, section Warnings and precautions and section Interactions). Nilotinib absorption (relative bioavailability) may be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

Distribution

Blood-to-plasma ratio of nilotinib is 0.68. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments.

Biotransformation/Metabolism

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum, primarily metabolized by CYP3A4. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

Elimination

After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in feces. Parent drug accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple dose PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high (%CV: 33% to 43%).

Linearity / non-linearity

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily systemic exposure to nilotinib of 400 mg twice-daily dosing at steady state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady state at a dose level of 400 mg twice daily was approximately 13.4% higher than with 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were approximately 15.7% and 14.8% higher following 400 mg twice daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily.

Steady-state conditions were essentially achieved by day 8. An increase in systemic exposure to nilotinib between the first dose and steady state was approximately 2-fold for the 400 mg once daily dosing and 3.8-fold for the 400 mg twice-daily dosing.

Bioavailability/bioequivalence studies

Single-dose administration of 400 mg of nilotinib, using 2 capsules of 200 mg whereby the content of each capsule was dispersed in one teaspoon of applesauce, was shown to be bioequivalent with a single dose administration of 2 intact capsules of 200 mg.

Clinical studies

Newly diagnosed Ph+ CML-CP

An open label, multicenter, randomized Phase III study was conducted to determine the efficacy of TASIGNA versus Glivec in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within six months of diagnosis and were previously

untreated for CML-CP, except for hydroxyurea and/or anagrelide. In addition, patients were stratified according to Sokal risk score at time of diagnosis.

Efficacy was based on a total of 846 patients (283 patients in the imatinib 400 mg once daily group, 282 patients in the nilotinib 300 mg twice daily group, 281 patients in the nilotinib 400 mg twice daily group).

Baseline characteristics were well balanced between the three groups. Median age was 46 years in the imatinib group and 47 years in both nilotinib groups, with 12.4%, 12.8% and 10.0% were ≥65 years of age in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily treatment groups, respectively. There were slightly more male than female patients in all groups (55.8%, 56.0% and 62.3% in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses reflect when patients completed 36 months and 60 months of treatment (or discontinued earlier). The median time on treatment was approximately 60 months in all three treatment groups. The median actual dose intensity was 400 mg/day in the imatinib group, 594 mg/day in the nilotinib 300 mg twice daily group and 773 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

Major molecular response (MMR)

The primary efficacy variable was MMR at 12 months after the start of study medication. MMR was defined as ≤ 0.1% BCR-ABL/ABL % by international scale measured by real-time quantitative polymerase chain reaction (RQ-PCR), which corresponds to a ≥ 3 log reduction of BCR-ABL transcript from standardized baseline.

The primary efficacy endpoint, MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (44.3% vs 22.3%, $p<0.0001$). The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group (42.7% vs 22.3%, $p<0.0001$), Table-6.

At the nilotinib recommended dose of 300 mg twice daily, the rate of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rates of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rate of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3%. The best overall MMR up to the cut-off date was achieved by 66.0% of patients in the nilotinib 300 mg twice daily group, 61.9% of patients in the nilotinib 400 mg twice daily group and 40.3% of patients in the imatinib group.

The MMR rate at 12, 24, 36, 48 and 60 months are presented in Table-6.

Table-6 MMR rate

	TASIGNA 300 mg twice daily N=282 n (%)	TASIGNA 400 mg twice daily N=281 n (%)	Imatinib 400 mg once daily N=283 n (%)
MMR at 12 months	125(44.3)[1]	120(42.7)[1]	63(22.3)
95% CI for response	[38.4,50.3]	[36.8,48.7]	[17.6, 27.6]
MMR at 24 months	174 (61.7)[1]	166 (59.1)[1]	106 (37.5)
95% CI for response	[55.8,67.4]	[53.1,64.9]	[31.8,43.4]
MMR at 36 months[2]	165 (58.5)[1]	161 (57.3)[1]	109 (38.5)
95% CI for response	[52.5,64.3]	[51.3,63.2]	[32.8,44.5]
MMR at 48 months[3]	169 (59.9)[1]	155 (55.2)	124 (43.8)
95% CI for response	[54.0,65.7]	[49.1,61.1]	[38.0,49.8]
MMR at 60 months[4]	177 (62.8)	172 (61.2)	139 (49.1)
95% CI for response	[56.8, 68.4]	[55.2, 66.9]	[43.2, 55.1]

[1] CMH test p-value for response rate (vs. Imatinib 400 mg) <0.0001

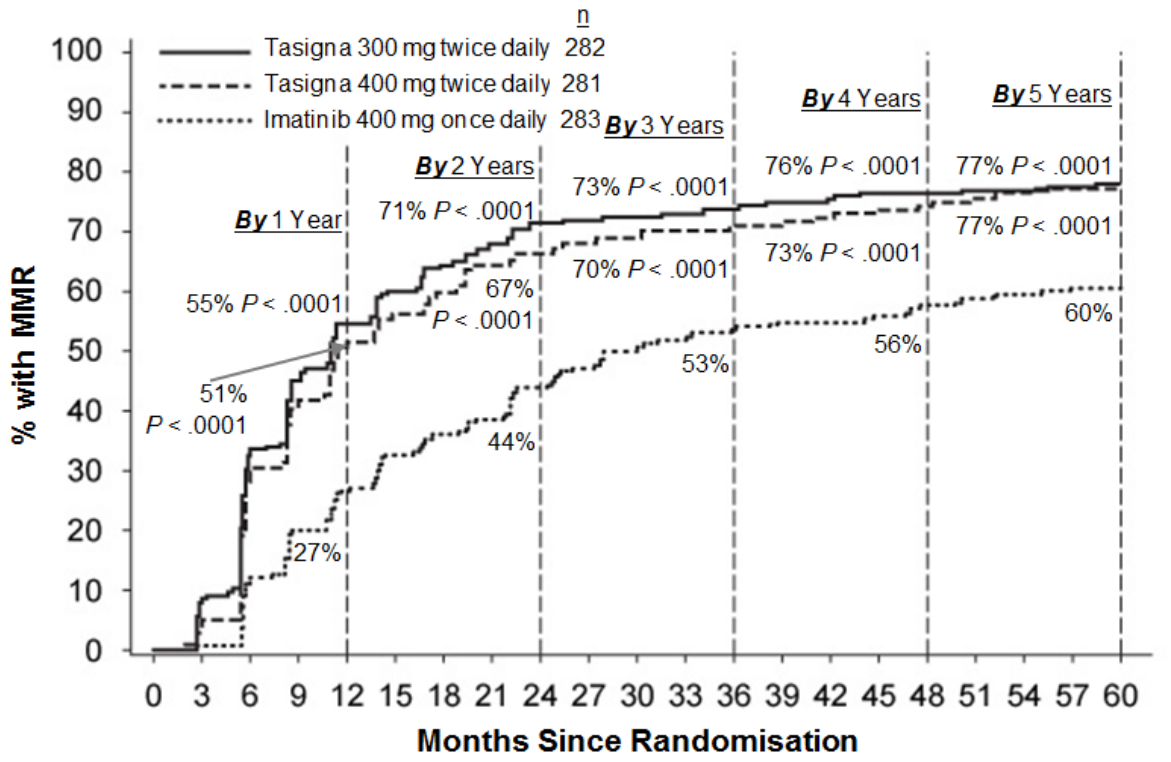
[2] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time point (n=175).

[3] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg BID group, 88 in the nilotinib 400 mg BID group and 119 in the imatinib group) due to missing/unevaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).

[4] Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 322 (38.1%) of all patients were not evaluable for MMR at 60 months (99 in the nilotinib 300mg BID group, 93 in the nilotinib 400 mg BID group and 130 in the imatinib group) due to missing/unevaluable PCR assessments (n=9), atypical transcripts at baseline (n=8), or discontinuation prior to the 60-month time point (n=305).

MMR rates by different time points (including patients who achieved MMR at or before those time points as responders) are presented in the cumulative incidence of MMR (Figure 1).

Figure 1 Cumulative Incidence of MMR



For all Sokal risk groups, the MMR rates at all time points remained consistently higher in the two nilotinib groups than in the imatinib group.

In a retrospective analysis, 91% (234/258) of patients on nilotinib 300 mg twice daily achieved BCR-ABL levels ≤10% at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels ≤10% at 3 months of treatment show a greater overall survival at 48 months compared to those who did not achieve this molecular response level (97% vs. 87% respectively [p=0.0116]).

Based on the Kaplan-Meier analyses of time to first MMR among all patients the probability of achieving MMR at different time points were higher in both nilotinib groups compared to the imatinib group (hazard ratio/HR=2.24 and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib, HR=1.92 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib).

The proportions of patients who had a molecular response of ≤ 0.01% and ≤ 0.0032% by International Scale (IS) at different time-points is presented in Table 6 and by different time-points are presented in Figure 2 and 3. Molecular response of ≤ 0.01% and ≤ 0.0032% by IS corresponds to a ≥ 4 log reduction and ≥ 4.5 log reduction, respectively, of BCR-ABL transcripts from a standardized baseline.

Table-7 Proportions of patients who had molecular response of ≤ 0.01% (4 log reduction and ≤ 0.0032% (4.5 log reduction)

	TASIGNA 300 mg twice daily N=282 (%)		TASIGNA 400 mg twice daily N=281 (%)		Imatinib 400 mg once daily N=283 (%)	
	≤ 0.01%	≤ 0.0032%	≤ 0.01%	≤ 0.0032%	≤ 0.01%	≤ 0.0032%
At 12 months	11.7	4.3	8.5	4.6	3.9	0.4
At 24 months	24.5	12.4	22.1	7.8	10.2	2.8
At 36 months	29.4	13.8	23.8	12.1	14.1	8.1
At 48 months	33.0	16.3	29.9	17.1	19.8	10.2
At 60 months	47.9	32.3	43.4	29.5	31.1	19.8

Figure 2 Cumulative incidence of molecular response of ≤ 0.01% (4-log reduction)

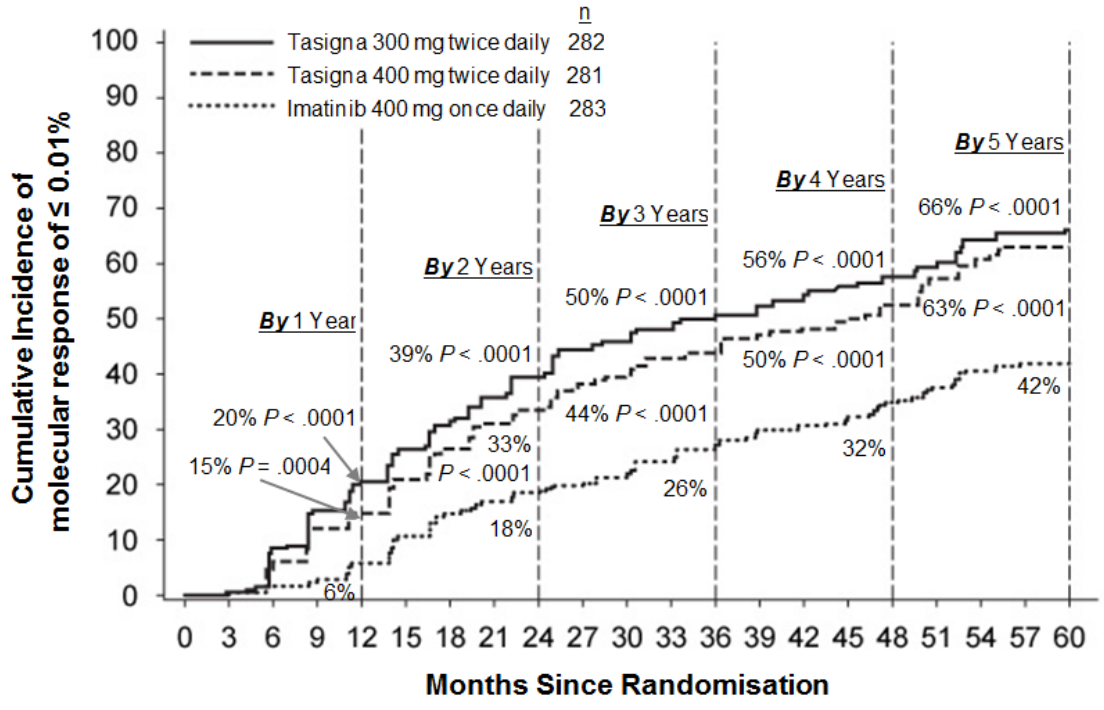
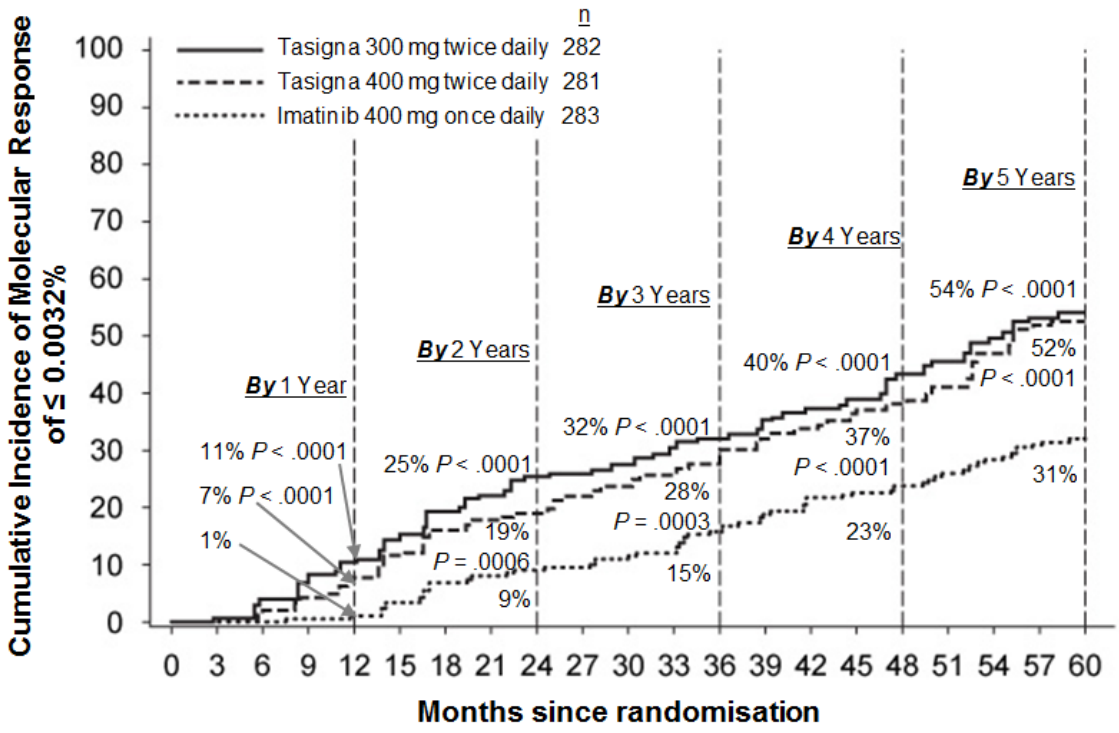


Figure-3 Cumulative incidence of molecular response of ≤ 0.0032% (4.5 log reduction)



Duration of MMR

Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who were maintaining response after 60 months among patients who achieved MMR were 93.4% (95% CI: 89.9% to 96.9%) in the nilotinib 300 mg twice daily group, 92.0% (95% CI: 88.2% to 95.8%) in the nilotinib 400 mg twice daily group and 89.1% (95% CI: 84.2% to 94.0%) in the imatinib 400 mg once daily group.

Complete cytogenetic response (CCyR)

CCyR was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. CCyR rate by 12 months (includes patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group, Table 7.

CCyR rate by 24 months (includes patients who achieved CCyR at or before the 24 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group.

Table-8 CCyR rate

	TASIGNA 300 mg twice daily N=282 n (%)	**TASIGNA 400 mg twice daily N=281 n (%)**	**Imatinib 400 mg once daily N=283 N (%)**
By 12 months			
Complete Cytogenetic Response	226 (80.1)	219 (77.9)	184 (65.0)
95% CI for response	[75.0,84.6]	[72.6,82.6]	[59.2,70.6]
CMH test p-value for response rate (vs. Imatinib 400 mg)	<0.0001	0.0005	
By 24 months			
Complete Cytogenetic Response	245 (86.9%)	238 (84.7%)	218 (77.0%)
95% CI for response	[82.4, 90.6]%	[79.9, 88.7]%	[71.7, 81.8]%
CMH test p-value for response rate (vs. Imatinib 400 mg)	0.0018	0.0160	

Duration of CCyR

Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response after 60 months among patients who achieved CCyR were 99.1% (95% CI: 97.9% to 100%) in the nilotinib 300 mg twice daily group, 98.7% (95% CI: 97.1% to 100%) in the nilotinib 400 mg twice daily group and 97.0% (95% CI: 94.7% to 99.4%) in the imatinib 400 mg once daily group.

Progression to AP/BC on treatment

Progression to AP/BC on treatment is defined as the time from the date of randomization to the first documented disease progression to AP/BC or CML-related death. Overall by the cut-off date, 17 patients progressed to AP or BC on treatment (2 in the nilotinib 300 mg twice daily group, 3 in the nilotinib 400 mg twice daily group and 12 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC at 60 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg twice daily (b.i.d) and imatinib, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg b.i.d and imatinib). No new events of progression to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 25 patients progressed to AP or BC on treatment by the cut-off date (3 in the nilotinib 300 mg twice daily group, 5 in the nilotinib 400 mg twice daily group and 17 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC including clonal evolution at 60 months were 98.7%, 97.9% and 93.2%, respectively (HR=0.1626 and stratified log-rank p=0.0009 between nilotinib 300 mg b.i.d and imatinib, HR = 0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg b.i.d and imatinib).

Overall survival (OS)

A total of 50 patients died during treatment or during the follow-up after discontinuation of treatment (18 in the nilotinib 300 mg twice daily group, 10 in the nilotinib 400 mg twice daily group and 22 in the imatinib 400 mg once daily group). Twenty-six (26) of these 50 deaths were related to CML (6 in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 60 months were 93.7%, 96.2% and 91.7%, respectively (HR=0.8026 and stratified log-rank p = 0.4881 between nilotinib 300 mg twice daily and imatinib, HR=0.4395 and stratified log-rank p = 0.0266 between nilotinib 400 mg twice daily and imatinib). Considering only CML-related deaths as events, the estimated rates of OS at 60 months were 97.7%, 98.5% and 93.8%, respectively (HR=0.3673 and stratified log-rank p = 0.0292 between nilotinib 300 mg twice daily and imatinib, HR=0.2411 and stratified log-rank p = 0.0057 between nilotinib 400 mg twice daily and imatinib).

Treatment discontinuation in newly diagnosed Ph+ CML-CP patients who have achieved a sustained deep molecular response

In an open-label, multicenter, single-arm study, 215 adult patients with Ph+ CML-CP treated with TASIGNA in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue TASIGNA treatment for an additional 52 weeks (TASIGNA consolidation phase). Of the 215 patients, 190 patients (88.4%) entered theTFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4 (BCR-ABL / ABL ≤0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL / ABL ≤0.0032% IS)
- No more than two assessments falling between MR4 and MR4.5 (0.0032% IS <BCR-ABL / ABL ≤0.01% IS).

In the set of patients who entered the TFR phase, the median age was 55 years. The proportion of female patients was 49.5%, and 21.1% of the patients were ≥65 years of age. The median actual dose intensity during the 52-week TASIGNA consolidation phase was 600.0 mg/day.

BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:

- Loss of MMR requiring patient to re-initiate TASIGNA treatment
- When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
- When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

Any patient with loss of MMR during the TFR phase re-initiated TASIGNA treatment at 300 mg twice daily or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance, within 5 weeks after the collection date of the blood sample demonstrating loss of MMR. Patients who required re-initiation of TASIGNA treatment were

monitored for BCR-ABL levels every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR.

The primary endpoint was the percentage of patients who were in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). Of the 190 patients who entered the TFR phase, 98 patients (51.6% [95% CI: 44.2, 58.9]) were in MMR in the TFR phase at 48 weeks.

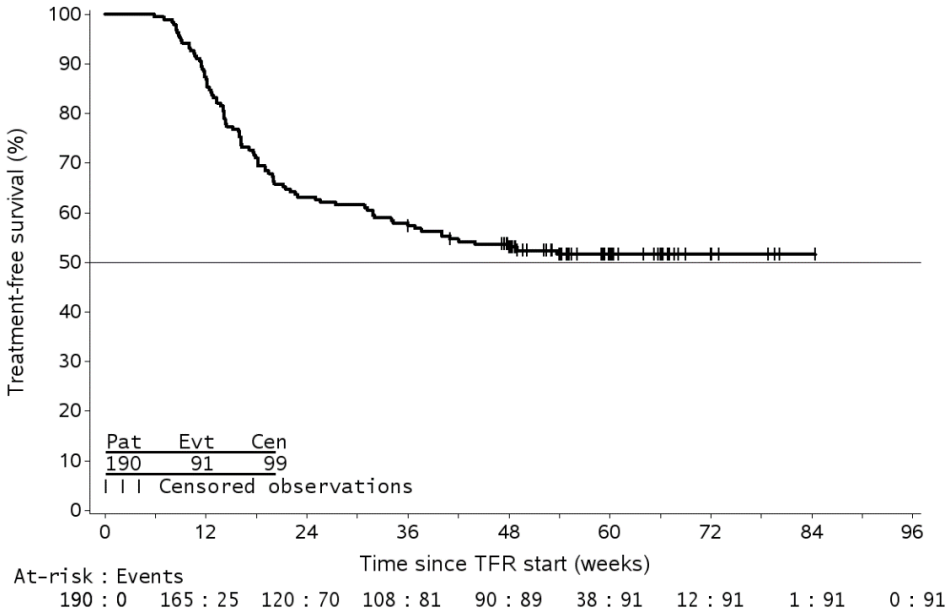
Eighty-eight patients (46.3%) discontinued from the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision, and subject decision, respectively. Among the 88 patients who discontinued the TFR phase due to loss of MMR, 86 patients restarted TASIGNA treatment and 2 patients permanently discontinued from the study.

Of the 86 patients who restarted treatment due to loss of MMR in the TFR phase, 85 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on TASIGNA to regain MMR and MR4.5 was 7.9 weeks (95% CI: 5.1, 8.0) and 13.1 weeks (95% CI: 12.3, 15.7), respectively. The KM estimated MMR rate at 24 weeks of re-initiation was 98.8% (95% CI: 94.2, 99.9). The KM estimated MR4.5 rate at 24 weeks of re-initiation was 90.9% (95% CI: 83.2, 96.0).

Among the 190 patients in the TFR phase, 99 patients (52.1%) did not have a treatment-free survival (TFS) event on or before the 48 month cut-off date, and were censored at the date of their last assessment prior to cut-off. The KM estimate of median TFS has not yet been reached (Figure 4).

Figure 4 **Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)**



Non-clinical safety data

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity (see section Pregnancy, lactation, females and males of reproductive potential), phototoxicity, carcinogenicity (rat and mice) studies.

Safety pharmacology and repeated dose toxicity

Nilotinib did not have effects on central nervous system (CNS) or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation. No effects were seen in ECG measurements in dogs or monkeys treated up to 39 weeks or in a special telemetry study in dogs.

Repeated dose toxicity studies in dogs up to 4 weeks duration and in cynomolgus monkeys up to 9 months duration, revealed the liver as the primary target organ of toxicity of nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity, and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible after a four week recovery period, the histological alterations only showed partial reversibility. Exposures at the lowest dose levels where the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys. In the 2-year rat carcinogenicity study, the major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

Carcinogenicity and mutagenicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of nilotinib.

In the 2-year rat carcinogenicity study there was no evidence of carcinogenicity upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level were representing approximately 2 to 3 times human daily steady-state exposure (based on AUC) to nilotinib at the dose of 800 mg/day. The major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

In the 26-week Tg.rasH2 mouse carcinogenicity study, in which nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level (NOEL) for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The major target organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or

severity of decreased lymphocytes).

Juvenile animal studies

In a juvenile development study, nilotinib was administered via oral gavage to juvenile rats from the first week postpartum through young adult (day 70 postpartum) at doses of 2, 6 and 20 mg/kg/day. Effects were limited to the dose of 20 mg/kg/day and consisted of reductions in body weight parameters and food consumption with recovery after dosing ceased. The NOEL in juvenile rats was considered to be 6 mg/kg/day. Overall, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Phototoxicity

Nilotinib was shown to absorb light in the UV-B and UV-A range, and to be distributed into the skin showing a phototoxic potential *in vitro*. However, no phototoxicity has been observed *in vivo*. Therefore the risk that nilotinib causes photosensitization in patients is considered very low.

Pharmaceutical information

Incompatibilities

Not applicable.

Shelf life

150 mg hard capsules

The expiry date is indicated on the packaging.

Special precautions for storage and other handling

Do not store above 30°C.

Store in the original package.

TASIGNA must be kept out of reach and sight of children.

Nature and contents of container

150 mg hard capsules: PA/AL/PVC blisters

Special precautions for disposal

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

Package

Tasigna capsule 150 mg: Box, 7 blisters @ 4 capsules Reg. No. DKIXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

Packed and released by Lek d.d., PE PROIZVODNJA LENDAVA, Lendava, Slovenia.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leaflet based on CDS amendment v2.2 – 18-May-2020 *and PP site transfer to Lek Lendava*