

Leaflet kemasan: Informasi bagi pengguna

CAMPTO 20 mg/mL konsentrat untuk larutan infus Irinotekan hidroklorida trihidrat

Bacalah brosur ini dengan saksama sebelum Anda menggunakan obat ini karena mengandung informasi yang penting untuk Anda.

- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, *sekali* pun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, berkonsultasilah dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala kemungkinan efek samping yang tidak tercantum di dalam leaflet ini. Lihat bagian 8.

Apa isi leaflet ini?

1. Nama produk
2. Deskripsi produk
3. Apa kandungan di dalam obat ini?
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5. Apa kegunaan obat ini?
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10. Efek yang tidak diinginkan
11. Tanda-tanda dan gejala-gejala overdosis
12. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?
13. Apa saja obat atau makanan lain yang harus dihindari selama menggunakan obat ini?
14. Bagaimana cara menyimpan obat ini?
15. Kapan sebaiknya Anda berkonsultasi dengan dokter?
16. Nama/logo produsen/importir/Pemegang Hak Pemasaran
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19. Peringatan khusus

1. Nama produk

CAMPTO 20 mg/mL konsentrat untuk larutan infus.

2. Deskripsi produk

CAMPTO adalah obat antikanker yang mengandung bahan aktif irinotekan hidroklorida trihidrat.

3. Apa kandungan obat ini?

Konsentrat ini mengandung 20 mg/mL irinotekan hidroklorida trihidrat (setara dengan 17,33 mg/mL irinotekan). Eksiipien: sorbitol, asam laktat, dan air untuk injeksi. pH larutan diatur menjadi 3,5 dengan natrium hidroksida. Vial CAMPTO berisi 40 mg atau 100 mg irinotekan hidroklorida trihidrat.

4. Kekuatan obat

20 mg/mL

5. Apa kegunaan obat ini?

Campto diindikasikan untuk pengobatan penderita kanker usus besar/rektum stadium lanjut atau metastasis:

- CAMPTO digunakan pada terapi kombinasi dengan 5-fluorouracil dan asam folinate (5-FU/FA) pada pasien yang sebelumnya belum pernah menjalani kemoterapi pada kanker stadium lanjut.
- CAMPTO digunakan sebagai terapi tunggal pada penderita kanker usus besar atau rektum metastasis yang penyakitnya mengalami kekambuhan atau bertambah parah setelah sebelumnya menjalani terapi awal menggunakan fluorouracil.
- CAMPTO digunakan pada terapi kombinasi dengan cisplatin untuk perawatan pasien dengan kanker paru sel kecil.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini?

Selalu gunakan obat ini dengan tepat sesuai petunjuk dokter Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

CAMPTO akan diberikan kepada Anda oleh petugas kesehatan.

Dokter akan menentukan dosis yang tepat bagi Anda.

Dokter Anda dapat merekomendasikan tes DNA sebelum Anda menerima dosis CAMPTO yang pertama. Beberapa orang secara genetik memiliki kecenderungan untuk mengalami efek samping tertentu akibat pengaruh obat ini.

Dosis CAMPTO yang akan Anda terima bergantung pada banyak faktor, di antaranya tinggi dan berat badan Anda, status kesehatan Anda secara umum atau masalah kesehatan lainnya, serta jenis kanker atau kondisi yang diobati. Dokter Anda akan menentukan dosis dan jadwal Anda.

CAMPTO diinjeksikan ke dalam pembuluh vena melalui rute intravena (IV). Anda akan menerima injeksi ini di lingkungan klinik atau rumah sakit. CAMPTO harus diberikan secara lambat, dan pemberian infus IV dapat membutuhkan waktu hingga 90 menit.

Anda mungkin akan diberi obat lain untuk mencegah muntah, mual, diare, dan efek samping lainnya selama Anda menjalani pengobatan dengan CAMPTO. Anda mungkin perlu terus menggunakan obat-obatan ini setidaknya satu hari setelah menerima injeksi CAMPTO.

Beri tahu perawat Anda jika Anda merasakan panas, nyeri, atau bengkak di sekitar jarum IV saat CAMPTO diinjeksikan. Jika obat keluar dari pembuluh vena maka dapat menyebabkan kerusakan jaringan. Jika Anda mengalami nyeri atau melihat adanya kemerahan atau pembengkakan di lokasi IV saat Anda menerima infus CAMPTO, segera beri tahu petugas kesehatan Anda.

Saat ini terdapat beberapa jadwal perawatan yang dianjurkan untuk CAMPTO. Biasanya diberikan satu kali setiap 3 minggu (CAMPTO diberikan sendiri), satu kali setiap 2 minggu

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(CAMPTO diberikan dalam kombinasi dengan kemoterapi 5FU/FA), atau diberikan dalam siklus 6 minggu berulang, yang terdiri atas Hari ke-1 dan ke-8 setiap 21 hari (CAMPTO diberikan dalam kombinasi dengan Cisplatin). Dosisnya bergantung pada sejumlah faktor, di antaranya jadwal perawatan, ukuran badan Anda, usia dan status kesehatan Anda secara umum, hitungan darah Anda, serta seberapa baik fungsi hati Anda, apakah Anda pernah menjalani radiasi di daerah perut/pelvis, dan apakah Anda mengalami efek samping apa pun seperti diare.

Hanya dokter yang dapat menilai durasi perawatan.

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

7. Apa yang harus dilakukan jika ada dosis terlewat?

Hubungi dokter Anda untuk mendapatkan instruksi jika Anda melewatkan janji temu untuk injeksi CAMPTO.

8. Kapan seharusnya Anda tidak menggunakan obat ini?

Jangan gunakan CAMPTO:

- jika Anda menderita inflammatory bowel disease dan/atau obstruksi perut kronis
- jika Anda alergi terhadap irinotekan hidroklorida trihidrat atau bahan lain yang terkandung dalam obat ini (dicantumkan di bagian 3 “**Apa kandungan di dalam obat ini**”)
- jika Anda sedang hamil atau menyusui
- jika kadar bilirubin Anda lebih tinggi dari 3 kali batas atas rentang normal
- jika Anda menderita kegagalan sumsum tulang yang berat
- jika kondisi Anda secara umum tergolong lemah (status kinerja WHO lebih tinggi daripada 2)

Jika Anda menerima CAMPTO dalam kombinasi dengan obat-obatan lainnya, pastikan bahwa Anda juga membaca leaflet kemasan obat-obatan lainnya tersebut mengenai kontraindikasi tambahan.

Kehamilan dan menyusui

Pasien perempuan yang berpotensi untuk hamil harus menggunakan kontrasepsi yang efektif selama dan setelah perawatan.

Kehamilan

Obat ini dapat menimbulkan masalah bagi janin jika diberikan pada saat pembuahan atau selama kehamilan.

Jika Anda hamil, menduga bahwa diri Anda hamil, atau sedang merencanakan kehamilan, mintalah saran dari dokter atau apoteker Anda sebelum menggunakan obat ini.

Menyusui

Belum ada penelitian yang dilakukan, namun demikian, obat ini dapat dikeluarkan bersama ASI dan berdampak terhadap bayi. Anda harus berhenti menyusui selama menjalani perawatan dengan obat ini.

Jika Anda sedang menyusui, mintalah saran dari dokter atau apoteker Anda sebelum menggunakan obat ini.

Mengemudi dan mengoperasikan mesin

Anda mungkin akan merasa pening dan/atau mengalami gangguan penglihatan dalam 24 jam pertama atau lebih setelah Anda menggunakan obat ini. Jangan mengemudi atau mengoperasikan mesin jika Anda merasakan efek samping ini.

CAMPTO mengandung sorbitol

Obat ini mengandung gula (sorbitol). Sorbitol adalah sumber fruktosa. Jika Anda (atau anak Anda) menderita intoleransi fruktosa yang diturunkan (HFI), suatu kelainan genetik yang langka, maka Anda (atau anak Anda) tidak boleh menerima obat ini. Pasien dengan HFI tidak dapat menguraikan fruktosa, sehingga dapat menimbulkan efek samping serius.

Anda harus memberi tahu dokter Anda sebelum menerima obat ini jika Anda (atau anak Anda) memiliki HFI, atau jika anak Anda tidak dapat lagi mengonsumsi makanan atau minuman manis karena mereka merasa mual, muntah, atau mengalami efek yang tidak nyaman seperti kembung, kram perut, atau diare.

9. Apa saja yang perlu diperhatikan saat menggunakan obat ini?

Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan CAMPTO

Berhati-hatilah saat menggunakan CAMPTO Penggunaan CAMPTO harus dibatasi dalam unit khusus untuk pemberian kemoterapi sitotoksik dan hanya boleh diberikan di bawah pengawasan dokter yang berkualifikasi dalam penggunaan kemoterapi antikanker.

Reaksi hipersensitivitas

Reaksi hipersensitivitas, termasuk reaksi anafilaktik atau anafilaktoid berat juga telah dilaporkan.

Efek immunosupresan / peningkatan kerentanan terhadap infeksi

Pemberian vaksin hidup atau yang dilemahkan pada pasien yang defisiensi imun (immunocompromised) terhadap obat-obat kemoterapi, termasuk irinotekan, dapat mengakibatkan infeksi serius atau fatal. Vaksinasi dengan vaksin hidup harus dihindari pada pasien yang menerima irinotekan. Vaksin mati atau yang tidak aktif dapat diberikan; namun, respons terhadap vaksin tersebut dapat dikurangi.

Diare

CAMPTO dapat menyebabkan diare, dan dalam beberapa kasus mungkin bersifat berat. Kondisi ini dapat dimulai beberapa jam atau beberapa hari setelah infus obat diberikan. Jika tidak ditangani, maka dapat menyebabkan dehidrasi dan ketidakseimbangan kimiawi serius, yang dapat mengancam jiwa. Dokter Anda akan meresepkan obat untuk membantu mencegah atau mengendalikan efek samping ini. Pastikan Anda segera mendapatkan obat yang dimaksud, sehingga sudah tersedia di rumah saat Anda membutuhkannya.

- Minum obat sesuai resep saat pertama kali Anda mengalami diare atau sering buang air besar.
- Minum air dalam jumlah banyak dan (atau) minuman asin (air berkarbonasi, soda, atau sup).
- Hubungi dokter atau perawat Anda jika Anda masih mengalami diare, khususnya jika berlanjut hingga lebih dari 24 jam, atau jika Anda merasa pusing, pening, atau jatuh pingsan.

Neutropenia (penurunan jumlah sel darah putih)

Obat ini dapat menurunkan hitungan sel darah putih Anda, terutama dalam beberapa minggu setelah obat diberikan. Kondisi ini meningkatkan risiko terkena infeksi. Pastikan Anda memberi tahu dokter atau perawat Anda secepatnya jika Anda mengalami tanda-tanda infeksi apa pun, seperti demam (38 °C atau lebih), dingin, nyeri saat berkemih, batuk, atau mengeluarkan dahak. Hindari berada di dekat orang yang sakit atau menderita infeksi. Langsung beri tahu dokter Anda jika Anda mengalami tanda-tanda infeksi.

Pemantauan darah

Dokter Anda mungkin akan melakukan tes darah terhadap Anda sebelum dan selama Anda menjalani perawatan untuk memeriksa efek obat terhadap hitungan darah atau terhadap kimia darah. Berdasarkan hasil tes, Anda bisa jadi memerlukan obat untuk mengatasi efek tersebut. Dokter mungkin juga perlu menurunkan atau menunda dosis berikutnya dari obat ini, atau bahkan menghentikannya sama sekali. Catat semua janji temu untuk kunjungan dokter dan tes laboratorium.

Obat ini dapat menurunkan hitungan platelet Anda dalam beberapa minggu setelah pemberian obat, sehingga dapat meningkatkan risiko perdarahan. Konsultasikan dengan dokter Anda sebelum meminum obat atau suplemen apa pun yang dapat memengaruhi kemampuan tubuh Anda untuk menghentikan perdarahan, seperti aspirin atau obat-obatan yang mengandung aspirin, warfarin, atau vitamin E. Segera beri tahu dokter Anda jika Anda mengalami lebam yang tidak biasa, perdarahan seperti mimisan, perdarahan gusi saat Anda menyikat gigi, atau feses berwarna hitam dan pekat.

Mual dan muntah

Anda dapat mengalami mual dan muntah pada hari Anda menerima obat ini atau dalam beberapa hari pertama sesudahnya. Dokter dapat memberi Anda obat sebelum perawatan dilakukan untuk membantu mencegah mual dan muntah. Dokter mungkin akan meresepkan obat-obatan antimual yang dapat Anda minum di rumah. Siapkan selalu obat-obatan ini untuk memudahkan Anda saat membutuhkannya. Hubungi dokter jika Anda tidak dapat mengonsumsi cairan melalui mulut dikarenakan mual dan muntah.

Sindrom kolinergik

Obat ini dapat memengaruhi bagian sistem saraf yang mengendalikan sekresi tubuh, sehingga menyebabkan kondisi yang dikenal dengan istilah sindrom kolinergik. Gejala-gejalanya dapat meliputi pilek, peningkatan sekresi air liur, air mata berlebihan, berkeringat, pipi memerah, kram perut, dan diare. Segera beri tahu dokter atau perawat Anda jika Anda melihat adanya gejala-gejala ini, karena tersedia obat-obatan yang dapat membantu mengendalikan kondisi tersebut.

Kelainan paru-paru

Meskipun jarang, tetapi pasien yang menggunakan obat ini dapat mengalami masalah serius pada paru-paru. Segera beri tahu dokter Anda jika Anda mengalami batuk yang baru terjadi atau batuk yang semakin parah, kesulitan bernapas, dan demam. Dokter mungkin perlu menghentikan perawatan Anda untuk mengatasi masalah ini.

Obat ini dapat meningkatkan risiko pembentukan bekuan darah besar di dalam pembuluh vena kaki atau paru-paru, yang dapat bergerak menuju bagian tubuh lainnya seperti paru-paru atau

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otak. Segera beri tahu dokter Anda jika Anda merasakan nyeri dada, napas pendek, atau pembengkakan, nyeri, kemerahan, atau rasa hangat di lengan atau kaki.

Peradangan usus kronis dan/atau sumbatan usus

Hubungi dokter Anda jika Anda merasakan nyeri di perut dan Anda kesulitan buang air besar, khususnya jika Anda juga merasa kembung dan kehilangan nafsu makan.

Terapi iradiasi

Jika Anda baru-baru ini menjalani perawatan dengan radioterapi pelvis atau abdomen, maka Anda berisiko lebih tinggi untuk mengalami supresi sumsum tulang. Beri tahu dokter Anda sebelum Anda memulai pengobatan dengan CAMPTO.

Fungsi ginjal

Telah dilaporkan terjadinya disfungsi ginjal.

Kelainan jantung

Beri tahu dokter Anda jika Anda menderita/pekerja menderita penyakit jantung atau jika sebelumnya Anda pernah menerima pengobatan antikanker. Dokter Anda akan memantau Anda dengan saksama dan berdiskusi dengan Anda mengenai cara-cara untuk mengurangi faktor risiko (misalnya merokok, tekanan darah tinggi, dan makanan berlemak).

Kelainan vaskular

CAMPTO sangat jarang dikaitkan dengan kelainan aliran darah (bekuan darah dalam pembuluh darah kaki dan paru-paru Anda) dan dapat dialami oleh pasien yang memiliki beberapa faktor risiko, kendati sangat jarang terjadi.

Geriatric

Rekomendasi dosis spesifik dapat berlaku untuk populasi ini, tergantung pada rejimen yang digunakan.

Gagal hati

Dokter Anda akan memantau fungsi hati Anda sebelum memulai pengobatan dan setiap bulannya, atau sesuai indikasi klinis.

Kanker Lambung

Pasien dengan kanker lambung terlihat mengalami peningkatan mielosupresi dan toksisitas lainnya ketika diberikan irinotecan. Dosis awal yang lebih rendah harus dipertimbangkan pada pasien ini.

Lainnya

Obat ini dapat menyebabkan rasa nyeri pada mulut atau bibir, sering kali di dalam beberapa minggu pertama setelah perawatan dimulai. Hal ini dapat menyebabkan rasa nyeri di dalam mulut, perdarahan, atau bahkan kesulitan makan. Dokter atau perawat Anda dapat menyarankan berbagai cara untuk mengurangi hal ini, seperti mengubah cara makan atau cara menyikat gigi Anda. Bila perlu, dokter dapat meresepkan obat untuk membantu mengatasi rasa nyeri tersebut.

Beri tahu dokter atau dokter gigi Anda bahwa Anda sedang menjalani terapi dengan obat ini jika Anda berencana menjalani pembedahan atau prosedur apa pun.

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Jika digunakan dalam kombinasi dengan obat antikanker lainnya untuk kondisi Anda, pastikan Anda juga membaca leaflet dari obat lainnya tersebut.

Jika Anda telah diberi tahu oleh dokter bahwa Anda memiliki intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum menggunakan produk medisinal ini.

10. Efek yang tidak diinginkan

Seperti semua obat-obatan yang ada, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Beberapa efek samping dapat berakibat serius. Anda harus segera menghubungi dokter jika Anda mengalami salah satu efek samping serius berikut ini.

Mintalah pertolongan medis darurat jika Anda mengalami tanda-tanda reaksi alergi ini: kaligata; kesulitan bernapas; pembengkakan wajah, bibir, lidah, atau tenggorokan.

Konsultasikan dengan dokter atau perawat Anda jika Anda mengalami gejala-gejala di bawah:

Efek samping yang sangat umum (kemungkinan dialami lebih dari 1 di antara 10 pasien) antara lain:

Gangguan pencernaan: Diare yang terjadi lebih dari 8 jam setelah pemberian obat; mual; muntah; diare yang terjadi kurang dari 8 jam setelah pemberian obat; nyeri perut; penurunan nafsu makan; rasa nyeri di mulut - peradangan mulut

Kelainan sel darah dan sistem limfatik: Penurunan jumlah sel darah putih (leukopenia dan neutropenia), sehingga menyebabkan mudah terserang infeksi; penurunan sel darah merah yang dapat membuat kulit Anda pucat dan menyebabkan Anda lemah atau sesak napas.

Gangguan umum: Merasa lemah dan kurangnya atau hilangnya kekuatan; demam

Gangguan metabolisme dan nutrisi: Penurunan berat badan; penurunan kadar air di dalam tubuh

Kelainan kulit dan jaringan di bawah kulit: Rambut rontok

Kelainan pembuluh darah: Gangguan pembuluh darah dikarenakan faktor pembekuan darah yang terganggu

Efek samping yang umum (kemungkinan dialami kurang dari 1 di antara 10 pasien) antara lain:

Infeksi dan infestasi: Infeksi

Gangguan pencernaan: Muntah, diare yang terjadi kurang dari 8 jam setelah pemberian obat, kesulitan atau lambatnya BAB; penurunan nafsu makan, peradangan membran mukosa

Kelainan sel darah dan sistem limfosit: Penurunan sel darah merah, penurunan jumlah trombosit dalam darah sehingga meningkatkan risiko perdarahan atau lebam

Gangguan umum: Merasa lemah dan kurangnya atau hilangnya kekuatan, demam, nyeri

Gangguan metabolisme dan nutrisi: Penurunan kadar air di dalam tubuh dan penurunan volume darah yang beredar di dalam tubuh

Gangguan sistem yang bekerja pada hati, pankreas, saluran empedu, dan kantong empedu: Kadar bilirubin yang tinggi dalam darah

Kelainan sistem respiratori, torasik, dan mediastinal: Sesak napas, kesulitan bernapas

Investigasi: Peningkatan kadar kreatinin

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Efek samping yang tidak umum (kemungkinan dialami kurang dari 1 di antara 100 pasien) antara lain:

Infeksi dan infestasi: Infeksi dalam aliran darah

Gangguan pencernaan: Gangguan pada rektum (bagian akhir saluran usus besar); infeksi saluran cerna oleh jamur *Monilinia*

Gangguan umum: Dingin; merasa tidak nyaman

Gangguan metabolisme dan nutrisi: Penurunan berat badan, rendahnya kadar kalium dalam darah sehingga dapat menyebabkan kelemahan otot, kedutan jantung atau irama jantung tidak normal; rendahnya kadar magnesium dalam darah

Kelainan kulit dan jaringan di bawah kulit: Ruam; tanda-tanda pada kulit

Gangguan sistem saraf: Cara berjalan tidak normal; kebingungan; sakit kepala

Kelainan fungsi jantung: Tekanan darah rendah; pingsan; gangguan sistem pembuluh darah dan jantung

Kelainan ginjal dan saluran kemih: Infeksi saluran kemih

Gangguan sistem reproduksi dan payudara: Nyeri payudara

Investigasi: Peningkatan alkaline fosfatase; peningkatan Gamma Glutamyl Trans Peptidase (GGTP), sebuah enzim yang ditemukan di dalam sel hati yang kadarnya tinggi jika terdapat kerusakan pada hati

Pengawasan pascapemasaran

Kelainan jantung

Kejadian iskemia miokardium teramati pada pasien setelah menjalani terapi irinotekan terutama pada pasien yang sudah mengidap penyakit jantung, memiliki faktor risiko lainnya yang diketahui untuk penyakit jantung, atau sebelumnya menjalani kemoterapi sitotoksik (pengobatan kanker mengandalkan kemampuan agen sitotoksik dalam mematikan atau merusak sel yang bereproduksi).

Kelainan saluran cerna

Dilaporkan adanya kasus obstruksi usus halus (penyumbatan yang menyebabkan makanan atau cairan tidak bisa melewati usus halus atau usus besar (kolon) Anda), ileus (penyumbatan yang menyebabkan makanan atau cairan tidak bisa melewati usus halus atau usus besar (kolon) Anda), megakolon (ukuran usus besar – bagian dari usus - lebih besar dibandingkan normal), atau perdarahan gastrointestinal (perdarahan saluran cerna, kehilangan darah dari mulut atau rektum), serta dilaporkan pula adanya kasus langka berupa kolitis (peradangan lapisan dalam usus besar), termasuk typhlitis (peradangan sekum – bagian dari usus), iskemia, dan kolitis ulseratif (peradangan usus besar Anda dengan pembatasan pasokan darah dan ulkus (luka)). Dalam beberapa kasus, terjadi komplikasi kolitis berupa ulserasi (ulkus (luka)), perdarahan, ileus, atau infeksi. Telah dilaporkan pula adanya kasus ileus tanpa didahului kolitis. Telah dilaporkan pula adanya kasus langka berupa perforasi usus halus (lubang pada dinding bagian dari usus halus).

Teramati pula adanya kasus langka berupa pankreatitis atau peningkatan enzim pankreas tanpa menunjukkan gejala.

Hipovolemia (baik hilangnya garam dan air atau penurunan volume darah)

Terdapat kasus langka berupa kerusakan ginjal dan gagal ginjal akut, umumnya pada pasien yang mengalami infeksi dan/atau mengalami penurunan volume yang drastis akibat toksisitas gastrointestinal (di seluruh saluran dari mulut hingga anus) yang berat.

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Teramati pula kasus yang jarang terjadi berupa insufisiensi ginjal (penurunan fungsi ginjal), hipotensi, atau kegagalan sirkulasi darah pada pasien yang mengalami episode dehidrasi yang diakibatkan oleh diare dan/atau muntah, atau sepsis.

Infeksi dan penginfeksian

Telah dilaporkan adanya infeksi bakteri, jamur, dan virus.

Kelainan sistem kekebalan tubuh

Reaksi hipersensitivitas, termasuk reaksi anafilaktik atau anafilaktoid berat (reaksi alergi atau respons imun yang berlebihan) juga telah dilaporkan.

Kelainan muskuloskeletal (termasuk sendi, ligamen, otot, saraf, tendon, dan struktur yang menopang anggota gerak, leher, dan punggung) dan kelainan jaringan penghubung (otot dan tulang)

Telah dilaporkan adanya efek di awal pengobatan, seperti kontraksi otot atau kram dan kesemutan/mati rasa.

Kelainan sistem saraf

Kelainan bicara, biasanya bersifat sementara, telah dilaporkan dialami oleh pasien yang diterapi dengan irinotekan; dalam beberapa kasus, bahkan dihubungkan dengan sindrom kolinergik (diproduksi melalui penghambatan transmisi saraf kolinergik pada lokasi reseptor muskarinik) yang teramati selama berlangsungnya atau tidak lama setelah pemberian infus irinotekan.

Kelainan respiratori (organ yang bertanggung jawab mengambil oksigen dan mengeluarkan karbon dioksida, organ primer sistem pernapasan adalah paru-paru), torasik (dada), dan mediastinal (mediastinum)

Penyakit paru interstitial (pneumonia interstitial) (gangguan yang menyebabkan jaringan parut (fibrosis) pada paru-paru, sehingga menyulitkan untuk bernapas) dan radang paru-paru pneumonitis (peradangan paru) yang ditunjukkan dalam bentuk bercak pada paru-paru juga telah teramati meskipun jarang. Telah dilaporkan adanya efek di awal perawatan seperti sesak

Pemeriksaan

Telah dilaporkan adanya kasus langka hiponatremia (konsentrasi natrium yang rendah di dalam darah) sebagian besar berkaitan dengan diare dan muntah. Peningkatan kadar transaminase (enzim di dalam hati) di dalam serum (yaitu AST dan ALT) tanpa adanya metastasis hati (tumor ganas yang sudah menyebar ke hati) progresif telah dilaporkan meskipun sangat jarang.

Melaporkan efek samping

Jika Anda mengalami efek samping apa pun, berkonsultasilah dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala kemungkinan efek samping yang tidak tercantum di dalam leaflet ini.

11. Tanda-tanda dan gejala-gejala overdosis

Gejala-gejala overdosis dapat mencakup beberapa efek samping serius yang tercantum dalam panduan pengobatan ini.

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

Hubungi dokter Anda atau segera datang ke unit gawat darurat di rumah sakit terdekat.

13. Apa saja obat atau makanan lain yang harus dihindari selama menggunakan obat ini?

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CAMPTO dapat berinteraksi dengan sejumlah obat dan suplemen, yang dapat meningkatkan atau menurunkan kadar obat dalam darah Anda. Beri tahu dokter atau apoteker Anda jika Anda sedang, belum lama ini, atau akan menggunakan obat mana pun berikut ini:

- Obat yang digunakan untuk mengobati kejang (karbamazepin, fenobarbital, dan fenitoin)
- Obat-obatan yang digunakan untuk mengobati infeksi jamur (ketokonazol)
- St. John's Wort (suplemen makanan herbal)
- Vaksin hidup atau vaksin hidup yang dilemahkan
- Obat-obatan untuk mengobati HIV (atazanavir)
- Obat-obatan yang digunakan untuk merelaksasi otot yang digunakan pada saat pembiusan umum dan pembedahan (suxamethonium)
- Bevacizumab (penghambat pertumbuhan pembuluh darah)
- Agen antineoplastik (obat antikanker) (penurunan pembentukan sel darah (mielosupresi) dan diare)
- Obat *dexamethasone* (penurunan limfosit di dalam darah (limfositopenia))
- Obat-obat diuretik

Jangan memulai atau menghentikan penggunaan obat apa pun selama Anda menjalani terapi CAMPTO tanpa berkonsultasi dengan dokter Anda terlebih dahulu.

Obat ini dapat menyebabkan diare serius. Cobalah untuk menghindari pencahar dan pelunak feses selama menggunakan obat ini.

Mungkin terdapat obat-obatan lain yang berinteraksi dengan CAMPTO. Konsultasikan dengan dokter, apoteker, atau perawat Anda tentang obat-obatan, herbal, dan suplemen Anda lainnya, dan apakah alkohol dapat menimbulkan masalah dengan obat ini.

14. Bagaimana cara menyimpan obat ini?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan menggunakan obat ini melebihi tanggal kedaluwarsa yang tertera pada dus. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Simpan pada suhu di bawah 30 °C. Simpan di dalam dus luar aslinya, jauhkan dari cahaya.

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

15. Kapan sebaiknya Anda berkonsultasi dengan dokter?

Jika Anda memiliki pertanyaan lebih lanjut atau Anda mengalami situasi yang sama seperti yang tercantum dalam leaflet ini, konsultasikan dengan dokter, apoteker, atau perawat Anda.

16. Nama/logo produsen/importir/Pemegang Hak Pemasaran

Diproduksi oleh:

Pfizer (Perth) Pty Limited, Australia

Diimpor oleh:

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Menggantikan: 19 Juli 2018
Disetujui oleh BPOM:
PT. Pfizer Indonesia,
Jakarta, Indonesia.

17. Penyajian

CAMPTO 40 mg: Vial polipropilena warna kuning bervolume 2 mL. Dus berisi 1 vial. Reg. No. DKI0955901349A1

CAMPTO 100 mg: Vial polipropilena warna kuning bervolume 5 mL. Dus berisi vial. Reg. No. DKI0955901349A1

18. Tanggal revisi

02/2022

19 Peringatan khusus

HARUS DENGAN RESEP DOKTER

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Informasi berikut ini ditujukan khusus bagi tenaga kesehatan profesional

Petunjuk untuk personel terkait penanganan CAMPTO secara aman

Seperti halnya zat antineoplastik lainnya, irinotekan harus disiapkan dan ditangani dengan penuh kehati-hatian. Penggunaanacamata pelindung, masker, dan sarung tangan harus dilakukan.

Jika CAMPTO mengenai kulit, cuci dengan segera dan menyeluruh menggunakan sabun dan air. Jika CAMPTO mengenai membran mukosa, cuci dengan segera dan menyeluruh menggunakan air.

Seperti halnya obat-obatan lain yang dapat diinjeksikan, CAMPTO harus disiapkan dalam kondisi aseptik.

Jika terlihat keruh atau terdapat kondensasi di dalam vial atau setelah pengenceran konsentrat, obat tidak boleh digunakan dan harus dibuang.

Penyiapan larutan untuk infus

Seperti halnya obat-obatan lain yang dapat diinjeksikan, larutan untuk infus CAMPTO harus disiapkan secara aseptik.

Jika Anda melihat ada endapan di dalam vial atau larutan untuk infus, buang produk sesuai prosedur standar untuk zat sitotoksik.

Ambil secara aseptik volume konsentrat CAMPTO yang telah dihitung untuk menyiapkan larutan untuk infus dari dalam vial ke dalam syringe dan pindahkan ke kantong atau botol infus berkapasitas 250 mL yang berisi larutan natrium klorida 0,9% (b/v) atau larutan infus glukosa 5% (b/v). Campur larutan untuk infus dalam kantong atau botol infus hingga merata dengan diputar-putar secara manual.

Jangan dicampur dengan obat-obatan lainnya.

Umur simpan

Simpan di bawah suhu 30 °C. Jauhkan dari paparan cahaya. Jauhkan dari jangkauan anak-anak.

Campuran yang Telah Diencerkan. Larutan akan stabil secara fisika dan kimia selama 24 jam pada suhu ruang dan pencahayaan pendar sekitar. Larutan yang diencerkan dalam Injeksi Dekstrosa 5% dan disimpan pada suhu lemari pendingin dan terlindung dari cahaya akan stabil secara fisika dan kimia selama 48 jam.

Penyimpanan campuran yang menggunakan Injeksi Natrium Klorida 0,9% dalam lemari pendingin tidak disarankan karena adanya insiden kemunculan partikulat yang terlihat, yang terjadi pada frekuensi rendah dan sporadis. Karena adanya kemungkinan kontaminasi mikroba selama pengenceran, maka disarankan agar campuran digunakan dalam waktu 24 jam jika disimpan di lemari pendingin atau dalam waktu 6 jam jika disimpan pada suhu ruang. Membekukan vial irinotekan atau campuran irinotekan dapat menimbulkan endapan obat dan harus dihindari.

Peringatan terhadap beberapa tanda penurunan kualitas

Jangan menggunakan CAMPTO jika Anda melihat endapan di dalam vial atau larutan yang diencerkan. Jika ini terjadi, produk harus dibuang sesuai dengan prosedur standar untuk pembuangan limbah sitotoksik. Jangan membuang obat melalui saluran pembuangan air. Tanyakan kepada apoteker perihal cara membuang obat yang sudah tidak lagi digunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

Pemberian

Untuk informasi tentang cara pemberian, baca Dokumen Produk Lokal untuk CAMPTO.

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Pembuangan

Setiap produk obat atau materi sampah harus dibuang sesuai dengan persyaratan setempat.

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Trade Name: CAMPTO
CDS Effective Date: June 28, 2021
Supersedes: September 17, 2019
Approved by BPOM:

PT. Pfizer Indonesia
Local Product Document

Generic Name: Irinotecan hydrochloride trihydrate
Trade Name: CAMPTO
CDS Effective Date: June 28, 2021
Supersedes: September 17, 2019

NAME OF THE MEDICINAL PRODUCT

CAMPTO

QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentrate for solution for infusion composition.

Active ingredient: irinotecan hydrochloride trihydrate.

The concentrate contains 20 mg/mL irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/mL irinotecan). Excipients: sorbitol, lactic acid and water for injections. The pH of the solution is adjusted to 3.5 with sodium hydroxide. Vials of CAMPTO contain 40 mg or 100 mg of irinotecan hydrochloride trihydrate.

CLINICAL PARTICULARS

Therapeutic indications

CAMPTO (irinotecan hydrochloride) is indicated for the treatment of patients with advanced colorectal cancer.

- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease;
- As a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

Irinotecan combination with cisplatin is indicated for treatment of patients with small-cell lung cancer.

Strictly follow the recommended dosage unless directed otherwise by the physician.

Posology and method of administration

For adults only. CAMPTO solution for infusion should be infused into a peripheral or central vein.

- **In monotherapy** (for previously treated patients):
The recommended dosage of CAMPTO is 350 mg/m² administered as an intravenous infusion over a 30- to 90-minute period every three weeks.
- **In combination therapy** (for previously untreated patients):

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Safety and efficacy of CAMPTO in combination with 5-fluorouracil (5 FU) and folinic acid (FA) have been assessed with the following schedule. The recommended dosage of CAMPTO is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and 5-fluorouracil.

Irinotecan in Combination with Cisplatin

The recommended starting dose is 65 mg/m² of irinotecan and 30 mg/m² of cisplatin. Cisplatin infused prior irinotecan. A lower starting dose of irinotecan may be considered for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer. Treatment should be given in repeated 6-week cycles, comprising Days 1 and 8, every 21 days.

Irinotecan should be administered as an intravenous infusion over 30 to 90 minutes.

Dosage adjustment

CAMPTO should be administered after appropriate recovery of all adverse events to Grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhea is fully resolved.

At the start of a subsequent infusion of therapy, the dose of CAMPTO, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events. With the following adverse events a dose reduction of 15% to 20% should be applied for CAMPTO and/or 5FU when applicable: hematological toxicity (Neutropenia Grade 4), febrile neutropenia (neutropenia Grade 3-4 and fever Grade 2-4), thrombocytopenia and leukopenia (Grade 4), non-hematological toxicity (Grade 3-4).

Duration of treatment

For both single-agent and combination-agent regimens, treatment with additional cycles of irinotecan may be continued indefinitely in patients who attain a tumor response or in patients whose cancer remains stable. Patients should be carefully monitored for toxicity and should be removed from therapy if unacceptable toxicity occurs that is not responsive to dose modification and routine supportive care.

Dose Modification Recommendations

The recommended dose modifications for irinotecan and cisplatin for the start of each cycle of therapy are described in Table 1, while recommended dose modifications during a cycle of therapy are described in Table 2.

Table 1. Dose Modifications at the Start of a New Cycle of the Cisplatin and Irinotecan (mg/m²) Combination Schedule - Based on the Worst Toxicity Observed in the Prior Cycle
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A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, and the platelet count has recovered to $\geq 100,000/\text{mm}^3$, serum creatinine ≤ 1.7 mg/dL or ≤ 130 $\mu\text{mol/L}$, and treatment-related non-hematologic toxicities (excluding

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alopecia) are resolved to ≤Grade 1. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.		
Toxicity NCI Grade ^a	Cisplatin ^b	Irinotecan ^c
HEMATOLOGIC		
Neutropenia/Thrombocytopenia Grade 0, 1, 2, or 3 Grade 4 Febrile neutropenia, ^d sepsis, thrombocytopenia requiring transfusion	Maintain dose level ↓ 1 dose level ↓ 2 dose level	Maintain dose level ↓ 1 dose level ↓ 2 dose level
NON-HEMATOLOGIC		
Diarrhea Grade 0, 1 or 2 Grade 3 or 4	Maintain dose level Maintain dose level	Maintain dose level ↓ 1 dose level
Vomiting Grade 0, 1 or 2 Grade 3 Grade 4	Maintain dose level ↓ 1 dose level ↓ 1 dose level	Maintain dose level Maintain dose level ↓ 1 dose level
Serum Creatinine ≤1.7 mg/dL >1.7-2.0 mg/dL >2.0 mg/dL	Maintain dose level ↓ 3 dose levels Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
Ototoxicity Grade 0 or 1 Grade 2 Grade 3 or 4	Maintain dose level ↓ 2 dose level Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
Neurotoxicity Grade 0 or 1 Grade 2 Grade 3 or 4	Maintain dose level ↓ 2 dose level Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
OTHER NON-HEMATOLOGIC TOXICITIES (Except Alopecia)		
Grade 0, 1 or 2 Grade 3 or 4	Maintain dose level ↓ 1 dose level	Maintain dose level ↓ 1 dose level
^a National Cancer Institute Common Toxicity Criteria ^b Cisplatin: dose level reductions = 5 mg/m ² decrements ^c Irinotecan: dose level reductions = 10 mg/m ² decrements ^d Febrile neutropenia is defined as in CTC version 2: temperature ≥38.5°C concomitant with an ANC <1.0 x 10 ⁹ /L.		

Table 2. Dose Modifications for Day 8 of the Cisplatin and Irinotecan (mg/m²) Combination Schedule Based on the Worst Toxicity Observed in the Prior Cycle		
Toxicity NCI Grade ^a	Cisplatin ^b	Irinotecan ^c
HEMATOLOGIC		
Neutropenia/Thrombocytopenia Grade 0 or 1 Grade 2 Grade 3 Grade 4	Maintain dose level ↓ 1 dose level ↓ 2 dose level Omit dose	Maintain dose level ↓ 1 dose level ↓ 2 dose level Omit dose

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Febrile neutropenia, ^d sepsis, thrombocytopenia requiring transfusion	Omit dose	Omit dose
NON-HEMATOLOGIC		
Diarrhea Grade 0 or 1 Grade 2 Grade 3 Grade 4	Maintain dose level Maintain dose level Maintain dose level Omit dose	Maintain dose level ↓ 1 dose level Omit dose Omit dose
Vomiting Grade 0, 1 or 2 Grade 3 Grade 4	Maintain dose level ↓ 1 dose level ↓ 1 dose level	Maintain dose level Maintain dose level ↓ 1 dose level
Serum Creatinine ≤1.7 mg/dL >1.7-2.0 mg/dL >2.0 mg/dL	Maintain dose level ↓ 2 dose levels Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
Ototoxicity Grade 0 or 1 Grade 2 Grade 3 or 4	Maintain dose level ↓ 1 dose level Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
Neurotoxicity Grade 0 or 1 Grade 2 Grade 3 or 4	Maintain dose level ↓ 1 dose level Discontinue cisplatin	Maintain dose level Maintain dose level Maintain dose level
OTHER NON-HEMATOLOGIC TOXICITIES (Except Alopecia)		
Grade 0 or 1 Grade 2, 3 or 4	Maintain dose level Omit dose	Maintain dose level Omit dose
^a National Cancer Institute Common Toxicity Criteria ^b Cisplatin: dose level reductions = 5 mg/m ² decrements ^c Irinotecan: dose level reductions = 10 mg/m ² decrements ^d Febrile neutropenia is defined as in CTC version 2: temperature ≥ 38.5°C concomitant with an ANC <1.0 x 10 ⁹ /L.		

Special populations

Elderly

No specific pharmacokinetic study has been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. These populations should require more intensive surveillance.

Patients with impaired hepatic function

In monotherapy: in patients with hyperbilirubinemia and prothrombin greater than 50%, the clearance of irinotecan is decreased and therefore, the risk of hematotoxicity is increased. Thus, frequent monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of CAMPTO is 350 mg/m².
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of CAMPTO is 200 mg/m².
- Patients with bilirubin beyond to 3 times the ULN should not be treated with CAMPTO (see Sections **Contraindications** and **Warning and precautions**).

No data are available in patients with hepatic impairment treated by CAMPTO in combination.

Patients with impaired renal functions

CAMPTO is not recommended for use in patients with impaired renal functions, as studies in this population have not been conducted.

Preparation and handling

As with other antineoplastic agents, CAMPTO must be prepared and handled with caution. The usage of glasses, mask and gloves is required. If CAMPTO solution or infusion solution come into contact with the mucous membranes, wash immediately with water.

Preparation for intravenous infusion administration

As with any other injectable drugs, the CAMPTO solution must be prepared aseptically. If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents. Aseptically withdraw the required amount of CAMPTO solution from the vial with a calibrated syringe and inject into a 250 mL infusion bag or bottle containing either 0.9% sodium chloride solution or 5% dextrose solution. The infusion is then thoroughly mixed by manual rotation.

Administration

CAMPTO solution for infusion should be infused into a peripheral or central vein. CAMPTO should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

Disposal

All material used for dilution and administration should be disposed of according to hospital standard procedure applicable to cytotoxic agents.

Contraindications

CAMPTO is contraindicated in patients with:

- A chronic inflammatory bowel disease and/or a bowel obstruction (see Section **Warning and precautions**).
- A history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of CAMPTO (see Section **Warning and precautions**).
- In pregnant or breast feeding women.
- In patient with bilirubin >3 times the ULN (see Section **Warning and precautions**).
- In patient with a severe bone marrow failure.
- In patients presenting a risk factor, particularly those with a WHO performance status >2 .

Warning and precautions

Administration. Irinotecan should be administered only under the supervision of a physician, who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Irinotecan will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:

- in patients presenting a risk factor, particularly those with a WHO performance status = 2.
- in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrheal treatment combined with high fluid intake at onset of delayed diarrhea). Strict hospital supervision is recommended for such patients.

Cholinergic symptoms. Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing (vasodilation), bradycardia, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea (i.e., diarrhea generally occurring during or within 8 hours of administration of irinotecan). These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more frequently with higher irinotecan doses. Therapeutic or prophylactic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing cholinergic symptoms.

Extravasation. While irinotecan is not a known vesicant, care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasations occur, flushing the site and application of ice is recommended.

Hepatic. In clinical studies, National Cancer Institute (NCI) Common Toxicity Criteria Grade 3 or 4 liver enzyme abnormalities have been observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases and are not clearly related to irinotecan.

Hematology. Irinotecan commonly causes neutropenia, leukopenia, and anemia, any of which may be severe and therefore, should not be used in patients with severe bone marrow failure. Serious thrombocytopenia is uncommon. In clinical studies, the frequency of NCI Grade 3 and 4 neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. There were no significant differences in the frequency of Grade 3 and 4 neutropenia by age or gender (see Section **Posology and method of administration**).

Neutropenic fever (concurrent NCI Grade 4 neutropenia and $\geq$ Grade 2 fever) occurred in fewer than 10% of patients in clinical studies; however, deaths due to sepsis

following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. Therapy with irinotecan should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below $1000/\text{mm}^3$. The dose of irinotecan should be reduced if clinically significant neutropenia occurs (see Section **Posology and method of administration**).

Patients with reduced UGT1A1 activity. The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form the inactive glucuronide metabolite SN-38G. This glucuronidation reaction is mediated primarily by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which is encoded by the UGT1A1 gene (see Section **Pharmacokinetic properties**). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1 28 variant allele. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced enzyme activity and increased systemic exposure to SN-38. Higher plasma concentrations of SN-38 are observed in individuals who are homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/6 genotype) versus patients who have one or two wild-type alleles.

Another specific polymorphism of UGT1A1 gene (that reduces the activity of this enzyme) is a missense mutation known as UGT1A1*6 variant.

Patients with UGT1A1*28 or *6 variants (especially if homozygous) are at increased risk of experiencing adverse events such as neutropenia and diarrhea. A reduced irinotecan starting dose should be considered for homozygous patients (see Section **Posology and method of administration**). In addition, *28 and *6 homozygous and heterozygous patients should be closely monitored for neutropenia and diarrhea.

The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on individual patient tolerance to treatment.

In order to identify patients at increased risk of experiencing neutropenia and diarrhea, UGT1A1 genotyping can be useful. More in detail, UGT1A1*28 genotyping can be useful in Caucasians, Africans and Latinos, UGT1A1*6 in East-Asians and combined UGT1A1*28 and *6 in Chinese and Japanese, since these are the populations in which these variants are more prevalent.

Hypersensitivity reactions. Hypersensitivity reactions, including severe anaphylactic/anaphylactoid reactions, have been reported.

Immunosuppressant effects/increased susceptibility to infections. Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including irinotecan, may result in serious or fatal infections. Vaccination with a

live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Late diarrhea. Late diarrhea (generally occurring more than 8 hours after administration of irinotecan) can be prolonged, may lead to dehydration, electrolyte imbalance, or sepsis and may be life-threatening.

In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of irinotecan. For patients starting treatment at the 125 mg/m² weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those patients treated at the 125 mg/m² weekly dose who experienced Grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. Results from a prospective study of the weekly dosage schedule did not demonstrate any difference in the rate of late onset diarrhea in patients ≥65 years of age than patients <65 years of age. However, patients ≥65 years of age should be closely monitored due to a greater risk of early diarrhea observed in this population. Colonic ulceration, sometimes with bleeding, has been observed in association with irinotecan-induced diarrhea.

Late diarrhea should be treated promptly with loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

The recommended dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours. Premedication with loperamide is not recommended. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated and should be given antibiotic support if they develop ileus, fever, or severe neutropenia. In addition to the antibiotic treatment, hospitalization is recommended for management of the diarrhea, in the following cases:

- Diarrhea associated with fever,
- Severe diarrhea (requiring intravenous hydration),
- Patients with vomiting associated with delayed (i.e., late) diarrhea,
- Diarrhea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

After the first treatment, subsequent weekly chemotherapy treatments should be delayed in patients until return of pre-treatment bowel function for at least 24 hours without need for anti-diarrhea medication. If NCI Grade 2, 3, or 4 diarrhea occurs, subsequent doses of irinotecan should be reduced within the current cycle (see Section **Posology and method of administration**).

Chronic inflammatory bowel disease and/or bowel obstruction. Patients must not be treated with CAMPTO until resolution of the bowel obstruction.

Nausea and vomiting. Irinotecan is emetogenic. Nausea and vomiting can be severe and usually occurs during or shortly after infusion of irinotecan. It is recommended that patients receive premedication with antiemetic agents. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed. Patients with vomiting associated with delayed diarrhea should be hospitalised as soon as possible for treatment.

Neurologic. Dizziness has been observed and may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Renal. Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhea. Rare instances of renal dysfunction due to tumor lysis syndrome have also been reported.

Respiratory. NCI Grade 3 or 4 dyspnea has been observed. The extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea is unknown. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest X-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease.

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Interstitial pulmonary disease can be fatal. Risk factors possibly associated with the development of interstitial pulmonary disease include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

Others. Since this product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Overdose. Single doses of up to 750 mg/m² irinotecan have been given to patients with various cancers. The adverse events in these patients were similar to those reported with the recommended dosages and regimens. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea. There is no known antidote for CAMPTO. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

Effects on ability to drive and use machines. Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of CAMPTO, and advised not to drive or operate machinery if these symptoms occur (see Section **Warning and precautions**).

Geriatric. Specific dosing recommendations may apply to this population depending upon the regimen used (see Section **Posology and method of administration**).

Hepatic insufficiency. In patients with hyperbilirubinemia, the clearance of irinotecan is decreased (see Section **Pharmacokinetic properties**) and therefore, the risk of hematotoxicity is increased. The use of irinotecan in patients with a serum total bilirubin concentration of $>3.0 \times$ institutional upper limit of normal (IULN) given as a single-agent on the once-every-3-weeks schedule has not been established (see Section **Posology and method of administration**). Liver function should be monitored before initiation of treatment and monthly, or as clinically indicated.

Irradiation therapy. Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in treating patients with extensive prior irradiation. Specific dosing recommendations may apply to this population depending upon the regimen used.

Performance status. Patients with poor performance status are at increased risk of irinotecan-related adverse events. Specific dosing recommendations for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 may apply depending upon the regimen used. Patients with performance status of 3 or 4 should not receive irinotecan. In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in clinical trials comparing these agents, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

Gastric cancer. Patients with gastric cancer appear to experience greater myelosuppression and other toxicities when given irinotecan. A lower starting dose should be considered in these patients.

Pregnancy and lactation

Pregnancy: There are no adequate and well-controlled studies of irinotecan in pregnant women. Irinotecan is teratogenic in rats and rabbits (see Section **Preclinical safety data**). Irinotecan may cause fetal harm when administered to a pregnant woman.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

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Due to the potential for genotoxicity advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment for 3 months after the last dose of irinotecan.

Lactation: The available data are limited to one patient only. Irinotecan and its active metabolite SN-38 were measured in the milk of one lactating patient. The effect on newborn/infants is unknown. Because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with irinotecan.

In rats, radioactivity appeared in the milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

Interactions

CYP3A4 and/or UGT1A1 inhibitors

Irinotecan and active metabolite SN-38 are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) (see Section **Pharmacokinetic properties**). Co-administration of irinotecan with inhibitors of CYP3A4 and/or UGT1A1 may result in increased systemic exposure to irinotecan and the active metabolite SN-38. Physicians should take this into consideration when administering irinotecan with these drugs.

Ketoconazole: Irinotecan clearance is greatly reduced in patients receiving concomitant ketoconazole, leading to increased exposure to SN-38. Ketoconazole should be discontinued at least 1 week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

Atazanavir sulfate: Co-administration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

CYP3A4 inducers

Anticonvulsants: Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to the active metabolite SN-38. Consideration should be given to starting or substituting non-enzyme-inducing anticonvulsants at least one week prior to initiation of irinotecan therapy in patients requiring anticonvulsant treatment.

*St. John's Wort (*Hypericum perforatum*):* Exposure to the active metabolite SN-38 is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be

discontinued at least 1 week prior to the first cycle of irinotecan, and should not be administered during irinotecan therapy.

Other interactions

Neuromuscular blocking agents: Interaction between irinotecan hydrochloride and neuromuscular blocking agents cannot be ruled out. Since CAMPTO has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonized.

Antineoplastic agents: The adverse effects of irinotecan, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

Dexamethasone: Lymphocytopenia has been reported in patients receiving irinotecan, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. However, serious opportunistic infections have not been observed and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

Laxatives: Laxative use during therapy with irinotecan is expected to worsen the incidence or severity of diarrhea.

Diuretics: Dehydration secondary to vomiting and/or diarrhea may be induced by irinotecan. The physician may wish to withhold diuretics during dosing with irinotecan and during periods of active vomiting or diarrhea.

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38.

Undesirable effects

Clinical studies

Adverse event data has been extensively collected and analyzed for the clinical studies program in metastatic colorectal cancer that recurred or progressed following 5-FU-based therapy (second-line) and are presented below (patient population described below). The adverse events for other indications are expected to be similar to those for second-line colorectal cancer.

Clinical studies of the 100- to 125-mg/m² single-agent weekly dosage schedule

The weekly dosage schedule of irinotecan was evaluated in three clinical studies of 304 patients with metastatic carcinoma of the colon or rectum that had recurred or

progressed following 5-FU-based therapy. Five (1.6%) deaths were potentially drug-related. These five patients experienced a constellation of medical events (myelosuppression, neutropenic sepsis without fever, small bowel obstruction, fluid accumulation, stomatitis, nausea, vomiting, diarrhea, and dehydration) that are known effects of irinotecan. Neutropenic fever, defined as NCI Grade 4 neutropenia and Grade 2 or greater fever, occurred in nine other patients; these patients recovered with supportive care.

Eighty-one (26.6%) patients were hospitalized for events judged to be related to administration of irinotecan. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting; neutropenia/leukopenia, with or without diarrhea and/or fever; and nausea and/or vomiting.

Adjustments in the dose of irinotecan were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with irinotecan because of adverse events.

Clinical studies of the 300- to 350-mg/m² once-every-3-week single-agent dosage schedule

A total of 316 patients with metastatic colorectal cancer whose disease had progressed following prior 5-FU therapy received irinotecan in two studies involving once-every-3-week administration. Three (1%) deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, Grade 4 diarrhea, and asthenia, respectively. Hospitalizations due to serious adverse events, whether or not related to irinotecan administration, occurred at least once in 60% of patients who received irinotecan and, 8% of patients treated with irinotecan discontinued treatment due to adverse events.

Listing of adverse events

The drug-related adverse events (NCI Grades 1-4) as judged by the investigator that were reported in greater than 10% of the 304 patients enrolled in the three studies of the weekly dosage schedule are listed by body system in descending order of frequency in Table 3.

Table 3. NCI Grade 1 to 4 Drug-related Adverse Events Observed in over 10% of Patients in Clinical Studies

<i>Gastrointestinal disorders:</i>	Late diarrhea, nausea, vomiting, early diarrhea, abdominal cramping/pain, anorexia, stomatitis
<i>Blood and lymphatic system disorders:</i>	Leukopenia, anemia, neutropenia
<i>General disorders and administration site conditions:</i>	Asthenia, fever
<i>Metabolism & nutrition disorders:</i>	Decreased weight, dehydration
<i>Skin and subcutaneous tissue disorders:</i>	Alopecia
<i>Vascular disorders:</i>	Thromboembolic events*

*Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

NCI Grade 3 or 4 adverse events reported in the clinical studies of the weekly and once-every-3-week-dosage schedules (N=620) are listed in Tables 4 to 6.

Table 4. NCI Grade 3 or 4 Drug-related Adverse Events Observed in over 10% of Patients in Clinical Studies

<i>Gastrointestinal disorders:</i>	Late diarrhea, nausea, abdominal cramping/pain
<i>Blood and lymphatic system disorders:</i>	Leukopenia, neutropenia
<i>Skin and subcutaneous tissue disorders:</i>	Alopecia

Table 5. NCI Grade 3 or 4 Drug-related Adverse Events Observed in 1% to 10% of Patients in Clinical Studies

<i>Infections and infestations:</i>	Infection
<i>Gastrointestinal disorders:</i>	Vomiting, early diarrhea, constipation, anorexia, mucositis
<i>Blood and lymphatic system disorders:</i>	Anemia, thrombocytopenia
<i>General disorders and administration site conditions:</i>	Asthenia, fever, pain
<i>Metabolism and nutrition disorders:</i>	Dehydration, hypovolemia
<i>Hepatobiliary disorders:</i>	Bilirubinemia
<i>Respiratory, thoracic and mediastinal disorders:</i>	Dyspnea
<i>Investigations:</i>	Increased creatinine

Table 6. NCI Grade 3 or 4 Drug-related Adverse Events Observed in Fewer than 1% of Patients in Clinical Studies

<i>Infections and infestations:</i>	Sepsis
<i>Gastrointestinal disorders:</i>	Rectal disorder, GI monilia
<i>General disorders and administration site conditions:</i>	Chills, malaise
<i>Metabolism and nutrition disorders:</i>	Decreased weight, hypokalemia, hypomagnesemia
<i>Skin and subcutaneous tissue disorders:</i>	Rash, cutaneous signs
<i>Nervous system disorders:</i>	Abnormal gait, confusion, headache
<i>Cardiac disorders:</i>	Hypotension, syncope, cardiovascular disorders
<i>Renal and urinary disorders:</i>	Urinary tract infection
<i>Reproductive system and breast disorders:</i>	Breast pain
<i>Investigations:</i>	Increased alkaline phosphatase, increased GGTP

The following additional drug-related events have been reported in clinical studies with irinotecan, but do not meet the criteria as defined above as either >10% drug-related NCI Grades 1-4 or as a NCI Grade 3 or 4 drug-related event: rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, bradycardia, dizziness, extravasation, tumor lysis syndrome, and colonic ulceration.

Post-marketing surveillance

Cardiac disorders

Myocardial ischemic events have been observed following irinotecan therapy predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease or previous cytotoxic chemotherapy (see also Table 3, thromboembolic events).

Gastrointestinal disorder

Infrequent cases of intestinal obstruction, ileus, megacolon, or gastrointestinal hemorrhage, and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis were reported. In some cases, colitis was complicated by ulceration, bleeding, ileus, or infection. Cases of ileus without preceding colitis have also been reported. Rare cases of intestinal perforation were reported.

Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypovolemia

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There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities.

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting, or sepsis.

Infections and infestations

Bacterial, fungal and viral infections have been reported.

Immune system disorders

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported (see Section **Warning and precautions**).

Musculoskeletal disorders and connective tissue disorders

Early effects, such as muscular contraction or cramps and paresthesia, have been reported.

Nervous system disorders

Speech disorders, generally transient in nature, have been reported in patients treated with irinotecan; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Respiratory thoracic and mediastinal disorders

Interstitial pneumonia and pneumonitis presenting as pulmonary infiltrates have rarely been observed. Early effects, such as dyspnea, have been reported (see Section **Warning and precautions**).

Investigations

Rare cases of hyponatremia mostly related with diarrhea and vomiting have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been very rarely reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class

Irinotecan hydrochloride is an antineoplastic agent of the topoisomerase I inhibitor class, clinically investigated as CPT-11. Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants, such as *Camptotheca acuminata*, or is chemically synthesized.

Mechanism of action

Irinotecan and its active metabolite SN-38 bind to the topoisomerase I – DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA

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synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. *In vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan. The precise contribution of SN-38 to the activity of irinotecan is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Pharmacokinetic properties

Absorption and distribution

After intravenous infusion in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the dose range of 50 to 350 mg/m², the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism & excretion

Irinotecan (CPT-11) is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan (CPT-11) can also undergo CYP3A4-mediated oxidative metabolism to several pharmacologically inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as the UGT1A1*28 polymorphism (see Section **Warning and precautions**). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative

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biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Pharmacokinetics in special populations

Geriatric: The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC₀₋₂₄ for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant.

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Race. The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency: (see Section **Posology and method of administration**). Irinotecan clearance is diminished in patients with hepatic dysfunction while relative exposure to the active metabolite SN-38 is increased. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in serum total bilirubin and transaminase concentrations.

Renal Insufficiency: (see Section **Posology and method of administration**). The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

Preclinical safety data

Toxicology

The acute intravenous toxicity of irinotecan in animals is shown below. Lethality was observed after single intravenous irinotecan doses of approximately 111 mg/kg in mice and 73 mg/kg in rats (approximately 2.6 and 3.4 times the recommended human dose of 125 mg/m², respectively). Death was preceded by cyanosis, tremors, respiratory distress, and convulsions. Subacute toxicity studies show that irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes).

Species	LD₅₀ (mg/kg)
Mouse	132-134
Rat	84-85
Dog	40-80

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Carcinogenicity/Mutagenicity

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan $C_{\max}$ and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m²) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Neither irinotecan nor SN-38 was mutagenic in the *in vitro* Ames assay. However, in the *in vitro* Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration-dependent manner. Additionally, in the *in vivo* mouse micronucleus assay, a single intraperitoneal dose of irinotecan over the dosage range of 2.5 to 200 mg/kg caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells.

Reproduction

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan $C_{\max}$ and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m²) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan $C_{\max}$ and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m²).

Radioactivity related to ¹⁴C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan $C_{\max}$ and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m²). Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan $C_{\max}$ and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m²) and in rabbits at 6 mg/kg/day (about one-half the recommended weekly human dose on a mg/m² basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

PHARMACEUTICAL PARTICULARS

Special precautions for storage

Store below 30°C. Store protected from light. Keep medicine out the reach of children.

Diluted Admixtures. The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5%

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Dextrose Injection and stored at refrigerated temperature and protected from light are physically and chemically stable for 48 hours.

Refrigeration of admixtures using 0.9% Sodium Chloride Injection is not recommended due to a low and sporadic incidence of visible particulates. Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated or within 6 hours if kept at room temperature. Freezing irinotecan vials or admixtures of irinotecan may result in precipitation of the drug and should be avoided.

Incompatibilities

Other drugs should not be added to the infusion solution.

Special precautions for disposal and other handling

Preparation

Irinotecan must be diluted prior to infusion in 5% Dextrose Injection, (preferred) or 0.9% Sodium Chloride Injection to a final concentration range of 0.12 to 2.8 mg/mL.

Handling

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan. The use of gloves is recommended. If irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

Presentation

CAMPTO 40 mg: 2 mL amber-coloured polypropylene vial. Box of 1 vial. Reg. No. DKI0955901349A1

CAMPTO 100 mg: 5 mL amber-coloured polypropylene vial. Box of 1 vial. Reg. No. DKI0955901349A1

ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

Manufactured by:

Pfizer (Perth) Pty Limited, Australia

Imported by:

PT. Pfizer Indonesia
Jakarta, Indonesia