leukin; ***Fr.:*** Proleukin; ***Ger.:*** Proleukin; ***Gr.:*** Proleukin; ***Hong Kong:*** Proleukin; ***Hung.:*** Proleukin; ***Irl.:*** Proleukin; ***Israel:*** Proleukin; ***Ital.:*** Proleukin; ***Jpn:*** Celeuk; Imunace; ***Mex.:*** Proleukin; ***Neth.:*** Proleukin; ***NZ:*** Proleukin; ***Pol.:*** Proleukin; ***Port.:*** Proleukin; ***Rus.:*** Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.:*** Chiron IL-2; ***Singapore:*** Proleukin†; ***Spain:*** Proleukin; ***Switz.:*** Proleukin; ***Turk.:*** Proleukin; ***UK:*** Proleukin; ***USA:*** Proleukin.

Ipilimumab *(USAN, rINN)*

Ipilimumabum; MDX-010; MDX-CTA-4. Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

Ипилимумаб

CAS — 477202-00-9.

Profile

Ipilimumab is an antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is under investigation for the treatment of melanoma and various solid tumours. Adverse effects include enterocolitis, hypophysitis, dermatitis, arthritis, uveitis, hepatitis, nephritis, and aseptic meningitis.

◊ References.

1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24:** 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12:** 864–72.

Iratumumab *(USAN, rINN)*

Iratumumabum; MDX-060. Immunoglobulin G1, anti-(tumor necrosis factor ligand superfamily member 8 (CD30 ligand)) (human monoclonal MDX-060 heavy chain), disulfide with human monoclonal MDX-060 light chain, dimer.

Иратумумаб

CAS — 640735-09-7.

Profile

Iratumumab is an anti-CD30 monoclonal antibody that is under investigation for the treatment of Hodgkin's disease. Reported adverse effects include a rise in liver transaminases, and acute respiratory distress syndrome.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekanhydroklorid; U-101440E. (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

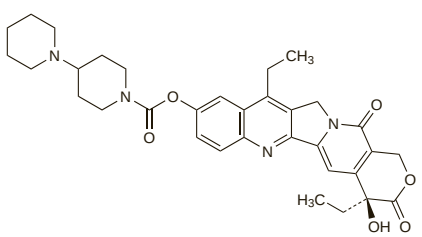
Иринотекана Гидрохлорид

$C_{33}H_{38}N_4O_6,HCl,3H_2O$ = 677.2.

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.



(irinotecan)

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Anaemia also occurs and, less commonly, thrombocytopenia. Gastrointestinal disturbances are common: acute diarrhoea, occurring within 24 hours of a dose, may be part of a cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, and miosis. These symptoms can be controlled with atropine. However a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Other adverse effects include nausea and vomiting, weakness, alopecia, and skin reactions. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions, interstitial pneumonia, pneumonitis, intestinal perforation, pancreatitis, muscular contraction or cramps, and paraesthesia.

Irinotecan should not be given to patients with inflammatory bowel disease. The risk of diarrhoea may be increased in the elderly and in patients who have had radiotherapy to the abdomen or pelvis. Radiotherapy also increases the risk of myelosuppression. Blood counts should be monitored weekly and liver function tests should be regularly performed.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, below).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, below.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients experiencing this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; **18:** 237.
2. Yang X, *et al.* Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; **12:** 1343–58.
3. Rothenberg ML, *et al.* Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; **19:** 3801–7.
4. Saliba F, *et al.* Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; **16:** 2745–51.
5. Lenfers BHM, *et al.* Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; **10:** 1251–3.
6. Savarese D, *et al.* Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; **18:** 450–1.
7. Ychou M, *et al.* Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; **23:** 143–8.
8. Pro B, *et al.* Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. *Invest New Drugs* 2001; **19:** 341–3.
9. Michael M, *et al.* Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; **22:** 4410–17.
10. Govindarajan R, *et al.* Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356:** 566–7.
11. Kehrer DFS, *et al.* Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; **7:** 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; while heterozygous patients may also be at risk, results of studies have been variable and such patients may tolerate normal initial doses of irinotecan. However, the most appropriate dose reduction in the homozygous population is not known. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m^2 daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity.

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44:** 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47:** 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22:** 1382–8.
4. Hahn KK, *et al.* Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; **63:** 2211–17.
5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24:** 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24:** 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25:** 2594–2600.

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94:** 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 144–5.

3. Ledermann JA, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 145–6.
4. Van Cutsem E, *et al.* Toxicity of irinotecan in patients with colorectal cancer. *N Engl J Med* 2001; **345:** 1351–2.
5. Falcone A, *et al.* Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients. *J Clin Oncol* 2001; **19:** 3456–62.

Smoking. A study found that tobacco smoking significantly affected the pharmacokinetics and toxicity of irinotecan.[1] Clearance of irinotecan was faster in smokers, and systemic exposure to the active metabolite SN-38 (see Pharmacokinetics, below) was almost 40% lower in smokers. This effect probably contributed to the significantly lower haematological toxicity seen in smokers; no significant difference in diarrhoea was seen between smokers and non-smokers. Smoking may induce cytochrome P450 isoenzyme CYP3A, or possibly affect carboxylesterase activity. The study did not determine an effect of smoking on the outcome of treatment with irinotecan. However, smokers may need a higher dose of irinotecan relative to non-smokers, since the lower exposure to irinotecan and SN-38 may indicate a potential risk of treatment failure.

1. van der Bol JM, *et al.* Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. *J Clin Oncol* 2007; **25:** 2719–26.

Thalidomide. A pharmacokinetic study found that the metabolism of irinotecan to SN-38 was significantly decreased by thalidomide. Despite reports of reduced gastrointestinal toxicity when these 2 drugs were given together (see Effects on the Gastrointestinal System, above), 3 out of 19 patients enrolled in the study had severe delayed diarrhoea after being given irinotecan with thalidomide.[1]

1. Allegrini G, *et al.* Irinotecan in combination with thalidomide in patients with advanced solid tumors: a clinical study with pharmacodynamic and pharmacokinetic evaluation. *Cancer Chemother Pharmacol* 2006; **58:** 585–93.

Pharmacokinetics

Irinotecan exhibits biphasic or triphasic pharmacokinetics, with a terminal half-life of about 14 hours. After intravenous doses it is hydrolysed by carboxylesterase in body tissues to active SN-38 (7-ethyl-10-hydroxycamptothecin). SN-38 exhibits a biphasic elimination profile with a terminal half-life of about 14 hours. Plasma protein binding for irinotecan and SN-38 is about 65% and 95%, respectively. SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is also partly metabolised by cytochrome P450 isoenzymes CYP3A4 and perhaps CYP3A5. More than 50% of an intravenous dose of irinotecan is excreted as unchanged drug, with about 30% in the faeces via the bile and about 20% in the urine.

◊ References.
1. Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet* 1997; **33:** 245–59.
2. Rivory LP. Metabolism of CPT-11: impact on activity. *Ann N Y Acad Sci* 2000; **922:** 205–15.
3. Mathijssen RH, *et al.* Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res* 2001; **7:** 2182–94.
4. Ma MK, McLeod HL. Lessons learned from the irinotecan metabolic pathway. *Curr Med Chem* 2003; **10:** 41–9.
5. Smith NF, *et al.* Pharmacogenetics of irinotecan metabolism and transport: an update. *Toxicol In Vitro* 2006; **20:** 163–75.

Uses and Administration

Irinotecan is a semisynthetic derivative of the alkaloid camptothecin, obtained from the shrub *Camptotheca acuminata*. The camptothecin derivatives are inhibitors of the enzyme topoisomerase I and thus interfere with the coiling and uncoiling of DNA during replication and prevent nucleic acid synthesis. This action is specific for S phase.

Irinotecan is used, alone or with fluorouracil-based chemotherapy, in the treatment of colorectal cancer (p.665). It is also indicated for use with cetuximab in the treatment of EGFR-expressing metastatic colorectal cancer, after the failure of other regimens containing irinotecan. It has been tried in the management of other solid tumours including those of the lung (p.668).

It is given as the hydrochloride, by intravenous infusion, in at least 250 mL of glucose 5%, or sodium chloride 0.9%. In the treatment of refractory colorectal malignancies one suggested single-agent dose regimen is irinotecan hydrochloride 125 mg/m^2 infused over 90 minutes once a week for 4 weeks, followed by a 2-week rest period. Additional courses may be given if required, with doses modified according to toxicity. Another regimen requires an initial dose of 350 mg/m^2 over 30 to 90 minutes repeated every 3 weeks and adjusted according to toxicity (for dosage in hepatic impairment, see below).

For the suggestion that initial doses should be modified to reduce toxicity in those with certain genotypes, see Genetic Factors, above.

Irinotecan may also be given as part of a regimen with fluorouracil and folinic acid in the first-line treatment of metastatic colorectal cancer. Numerous regimens exist. The irinotecan hydrochloride component of the course may be given at a dose of 180 mg/m^2 over 30 to 90 minutes every 2 weeks. Alternatively, 125 mg/m^2 may be given weekly, usually on days 1, 8, 15, and 22 of a 42-day cycle. (For reference to toxicity from such regimens see under Interactions, above.)

Treatment cycles may be continued indefinitely as long as patients continue to benefit.

In the treatment of EGFR-expressing metastatic colorectal cancer, when used with cetuximab, irinotecan is given usually at the same dose as was used in the last cycles of the previous irinotecan-containing regimen; irinotecan should not be given for at least 1 hour after the end of the cetuximab infusion.

A formulation of irinotecan with hyaluronic acid is being developed.

◊ References.
1. Douillard JY, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355:** 1041–7. Correction. *ibid.*; 1372.
2. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
3. Rothenberg ML. Irinotecan (CPT-11): recent developments and future directions—colorectal cancer and beyond. *Oncologist* 2001; **6:** 66–80.
4. Saltz LB, *et al.* Irinotecan plus fluorouracil/leucovorin for metastatic colorectal cancer: a new survival standard. *Oncologist* 2001; **6:** 81–91.
5. Cunningham D, *et al.* Optimizing the use of irinotecan in colorectal cancer. *Oncologist* 2001; **6** (suppl 4): 17–23.
6. Vanhoefer U, *et al.* Irinotecan in the treatment of colorectal cancer: clinical overview. *J Clin Oncol* 2001; **19:** 1501–18.
7. Douillard JY, *et al.* Update on European adjuvant trials with irinotecan for colorectal cancer. *Oncology (Huntingt)* 2002; **16** (suppl 3): 13–15.
8. Ulukan H, Swaan PW. Camptothecins: a review of their chemotherapeutic potential. *Drugs* 2002; **62:** 2039–57.
9. Pizzolato JF, Saltz LB. The camptothecins. *Lancet* 2003; **361:** 2235–42.
10. Glimelius B. Benefit-risk assessment of irinotecan in advanced colorectal cancer. *Drug Safety* 2005; **28:** 417–33.
11. Fuchs C, *et al.* Irinotecan in the treatment of colorectal cancer. *Cancer Treat Rev* 2006; **32:** 491–503.
12. Sato T, *et al.* Treatment of advanced or recurrent colorectal cancer with irinotecan in Japan and elsewhere. *Expert Opin Pharmacother* 2008; **9:** 1223–8.

Administration in hepatic impairment. In patients with hyperbilirubinaemia, the clearance of irinotecan is decreased, exposure to the active metabolite SN-38 is increased, and the risk of haematological toxicity is increased. US licensed product information recommends a reduction in the initial dose of irinotecan for those patients with increased bilirubin concentrations. However, doses in patients with bilirubin greater than 2 mg/100 mL cannot be determined due to insufficient data.

In the UK, licensed product information recommends the following dosage reduction for monotherapy regimens in which irinotecan hydrochloride is normally given at 350 mg/m^2 every 3 weeks (see Uses and Administration, above):

- in patients with bilirubin up to 1.5 times the upper limit of normal range (ULN), no dosage reduction is considered necessary and irinotecan hydrochloride 350 mg/m^2 is recommended;
- in patients with bilirubin ranging from 1.5 to 3 times the ULN, irinotecan hydrochloride 200 mg/m^2 may be given;
- in patients with bilirubin over 3 times the ULN, the use of irinotecan is not recommended.

Preparations

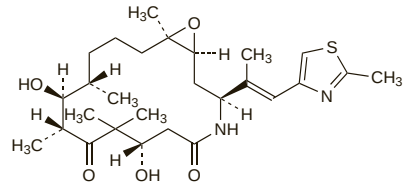
Proprietary Preparations (details are given in Part 3)
Arg.: Biotecan; Camptosar; CPT†; Efixano; Irenax; Irinogen; Itoxaril; Kebirtecan; Pipetecan; Satigene; Sibudan; Trinotecan; Winol; ***Austral.:*** Camptosar; ***Austria:*** Campto; ***Belg.:*** Campto; ***Braz.:*** Biotecan; Camptosar; Irenax; Tecnotecan; ***Canad.:*** Camptosar; ***Chile:*** Camptosar; Linatecan; ***Cz.:*** Campto; Canri; ***Denm.:*** Campto; ***Fin.:*** Campto; ***Fr.:*** Campto; ***Ger.:*** Campto; ***Gr.:*** Campto; ***Hong Kong:*** Campto; ***Hung.:*** Campto; ***India:*** Irinotel; ***Indon.:*** Campto; ***Irl.:*** Campto; ***Israel:*** Campto; ***Ital.:*** Campto; ***Malaysia:*** Campto; ***Mex.:*** Camptosar; Daritex A; Terican; ***Neth.:*** Campto; ***Norw.:*** Campto; ***NZ:*** Camptosar; ***Philipp.:*** Campto; ***Pol.:*** Campto; ***Port.:*** Campto; Faultenocan; ***Rus.:*** Campto (Кампто); Iriten (Иритен); Irnocam (Ирнокам); ***S.Afr.:*** Campto; ***Singapore:*** Campto; ***Spain:*** Campto; ***Swed.:*** Campto; ***Switz.:*** Campto; ***Thai.:*** Campto; Irinotel; ***Turk.:*** Campto; ***UK:*** Campto; ***USA:*** Camptosar; ***Venez.:*** Camptosar; Elinatecan.

Ixabepilone *(USAN, rINN)*

Azaepothilone B; BMS-247550-01; Ixabepilona; Ixabépilone; Ixabepilonum. (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.

Иксабепильон

$C_{27}H_{42}N_2O_5S$ = 506.7.
CAS — 219989-84-1.
ATC — L01DC04.
ATC Vet — QL01DC04.



Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Peripheral neuropathy is common with ixabepilone, and dose reduction, or delaying or stopping treatment may be necessary (see Uses and Administration, below). Dose-dependent myelosuppression can occur, manifested mainly as neutropenia; febrile neutropenia and fatalities have been reported. Frequent blood counts are recommended. Ixabepilone is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance; patients should be premedicated with a histamine H_1- and histamine H_2-antagonist about 1 hour before infusion. Therapy should be stopped if a hypersensitivity reaction occurs, and symptomatic treatment given. Subsequent cycles may be given with additional corticosteroid therapy, and extension of the infusion time should be considered.

Other adverse effects include gastrointestinal disturbances, anorexia, myalgia, arthralgia, fatigue, alopecia, insomnia, headache, taste disorders, dizziness, increased lachrymation, dyspnoea, cough, skin rashes, nail disorders, palmar-plantar erythrodysesthesia syndrome, pruritus, skin exfoliation or hyperpigmentation, and hot flushes.

Interactions

Ixabepilone undergoes extensive metabolism by cytochrome P450 isoenzyme CYP3A4. Inhibitors of CYP3A4, such as ketoconazole, can increase exposure to ixabepilone. Conversely, CYP3A4 inducers can reduce exposure to ixabepilone. Use of ixabepilone with strong inhibitors or inducers of CYP3A4 should be avoided. If strong inhibitors are used, dose adjustments may be required (see Uses and Administration, below). Grapefruit juice may also increase plasma concentrations of ixabepilone and should be avoided. St John's wort may decrease plasma concentrations of ixabepilone unpredictably and should also be avoided.

Pharmacokinetics

Ixabepilone is extensively distributed. Plasma protein binding is about 67 to 77%. It is extensively metabolised in the liver, mainly by oxidation via cytochrome P450 isoenzyme CYP3A4. It is eliminated mainly as metabolites; about 86% of a dose is eliminated within 7 days, 65% in faeces, and 21% in the urine. The terminal elimination half-life is reported to be about 52 hours.

Uses and Administration

Ixabepilone is an analogue of the epothilone compound patupilone (p.761) that is used for the treatment of patients with metastatic or locally advanced breast cancer. It is given as monotherapy in those whose tumours are resistant or refractory to anthracyclines, taxanes, and capecitabine. Ixabepilone is also used with capecitabine in those whose tumours are resistant to anthracycline and taxanes, or in those with cancer resistant to taxanes, and for whom further anthracycline therapy is contraindicated.

The recommended dose of ixabepilone is 40 mg/m^2 given by intravenous infusion over 3 hours every 3 weeks. Patients with a body-surface greater than 2.2 m^2 should be dosed as calculated for 2.2 m^2. Ixabepilone is diluted with lactated Ringer's solution to a final concentration of 200 to 600 micrograms/mL before infusion.

Doses are adjusted for toxicity. If moderate or severe neuropathy, or any severe toxicity (other than neuropathy) occurs, the dose should be decreased by 20%. If severe neuropathy lasts 7 days or more, or any disabling toxicity occurs, therapy should be stopped. If the neutrophil count falls below 500 cells/mm^3 for 7 days or more, if platelets fall below 25 000 cells/mm^3 (or below 50 000 cells/mm^3 with bleeding), or if febrile neutropenia occurs, the dose should be decreased by 20%. If toxicities recur, an additional 20% dose reduction should be made. Patients should not begin a new cycle of treatment unless the neutrophil count is at least 1500 cells/mm^3, the platelet count is at least 100 000 cells/mm^3, and non-haematological toxicities have improved to grade 1 (mild) or resolved.