be given as pegaspargase, in doses of 2500 units/m^2 every 14 days, preferably by intramuscular injection although the intravenous route may also be used.

Asparaginase is not generally used alone as an induction agent but doses of 200 units/kg daily have been given intravenously for 28 days to adults and children. If pegaspargase is used alone doses are the same as for combination regimens. Children appear to tolerate asparaginase better than adults.

Although not entirely reliable, an intradermal test dose of about 2 units has been recommended in the USA, to test for hypersensitivity, before treatment with colaspase or where more than a week has elapsed between doses. Desensitisation has been advocated if no alternative antineoplastic treatment is available. Anaphylaxis with crisantaspase is stated to be rare; however, in the UK if there has been an interruption in treatment, therapy should be resumed with a low dose of 10 units/kg daily and increased to the full dose over 5 days if tolerated. A test dose is not advocated, although reference to local leukaemia protocols is recommended. The incidence of hypersensitivity is also lower in patients given pegaspargase, and again a test dose is not advocated. Pegaspargase has been successfully used in patients hypersensitive to the native enzyme.

For intravenous use a solution of asparaginase in Water for Injections or sodium chloride 0.9% should be given over not less than 30 minutes through a running infusion of sodium chloride 0.9% or glucose 5%. When given intramuscularly no more than 2 mL of a solution in sodium chloride 0.9% should be injected at a single site.

◊ References.

1. Muller HJ, Boos J. Use of L-asparaginase in childhood ALL. *Crit Rev Oncol Hematol* 1998; **28:** 97–113.
2. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol* 1999; **457:** 621–9.
3. Abshire TC, *et al.* Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 2000; **96:** 1709–15.
4. Avramis VI, Panosyan EH. Pharmacokinetic/pharmacodynamic relationships of asparaginase formulations: the past, the present and recommendations for the future. *Clin Pharmacokinet* 2005; **44:** 367–93.
5. Fu CH, Sakamoto KM. PEG-asparaginase. *Expert Opin Pharmacother* 2007; **8:** 1977–84.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Kidrolase; L-Asp†; Oncaspar; ***Austral.:*** Leunase; ***Belg.:*** Paronal; ***Braz.:*** Elspar; ***Canad.:*** Kidrolase; ***Cz.:*** Erwinase†; Kidrolase; ***Denm.:*** Erwinase†; ***Fin.:*** Erwinase†; ***Fr.:*** Kidrolase; ***Ger.:*** Erwinase†; Oncaspar; ***Gr.:*** Erwinase; Oncaspar; ***Hong Kong:*** Elspar†; Leunase; ***India:*** Leunase; ***Indon.:*** Leunase; ***Irl.:*** Erwinase; ***Israel:*** Kidrolase; ***Jpn:*** Leunase; ***Malaysia:*** Erwinase†; Leunase; ***Mex.:*** Leunase; ***Neth.:*** Erwinase; Paronal; ***NZ:*** Erwinase; Leunase; ***Philipp.:*** Leunase; ***Pol.:*** Oncaspar; ***Port.:*** Erwinase; ***Rus.:*** Oncaspar (Онкаспар); ***S.Afr.:*** Laspar; ***Singapore:*** Erwinase†; Leunase; ***Swed.:*** Erwinase; ***Thai.:*** Erwinase†; Leunase; ***Turk.:*** Leunase; ***UK:*** Erwinase; ***USA:*** Elspar; Oncaspar.

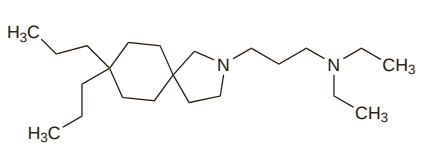
Atiprimod *(rINN)*

Atiprimodum. 2-[3-(Diethylamino)propyl]-8,8-dipropyl-2-azaspiro[4.5]decane.

Атипримод

$C_{22}H_{44}N_2$ = 336.6.

CAS — 123018-47-3 (atiprimod); 130065-61-1 (atiprimod hydrochloride); 183063-72-1 (atiprimod maleate).



Profile

Atiprimod is an antineoplastic that is under investigation for the treatment of carcinoid tumours and multiple myeloma.

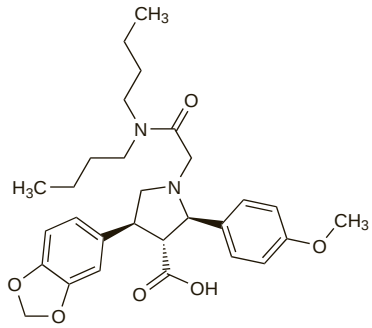
Atrasentan Hydrochloride *(USAN, rINNM)*

A-147627.1; Abbott-147627; ABT-627; Atrasentan, Chlorhydrate d'; Atrasentani Hydrochloridum; Hidrocloruro de atrasentán. (2*R*,3*R*,4*S*)-1-[(Dibutylcarbamoyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid hydrochloride.

Атразентана Гидрохлорид

$C_{29}H_{38}N_2O_6$,HCl = 547.1.

CAS — 173937-91-2 (atrasentan); 195733-43-8 (atrasentan hydrochloride).



(atrasentan)

Profile

Atrasentan hydrochloride is a selective endothelin-A receptor antagonist that inhibits the effect of endothelin-1, a protein that may be involved in cancer progression. It is under investigation in the treatment of prostate cancer, and has been tried in other malignant neoplasms.

◊ References.

1. Samara E, *et al.* Single-dose pharmacokinetics of atrasentan, an endothelin-A receptor antagonist. *J Clin Pharmacol* 2001; **41:** 397–403.
2. Carducci MA, *et al.* Atrasentan, an endothelin-receptor antagonist for refractory adenocarcinomas: safety and pharmacokinetics. *J Clin Oncol* 2002; **20:** 2171–80.
3. Carducci MA, *et al.* Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial. *J Clin Oncol* 2003; **21:** 679–89.
4. Zonnenberg BA, *et al.* Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: an endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 2003; **9:** 2965–72.
5. Ryan CW, *et al.* Dose-ranging study of the safety and pharmacokinetics of atrasentan in patients with refractory malignancies. *Clin Cancer Res* 2004; **10:** 4406–11.
6. Michaelson MD, *et al.* Randomized phase II study of atrasentan alone or in combination with zoledronic acid in men with metastatic prostate cancer. *Cancer* 2006; **107:** 530–5.
7. Carducci MA, *et al.* Atrasentan Phase III Study Group Institutions. A phase 3 randomized controlled trial of the efficacy and safety of atrasentan in men with metastatic hormone-refractory prostate cancer. *Cancer* 2007; **110:** 1959–66.
8. Chiappori AA, *et al.* Phase I/II study of atrasentan, an endothelin A receptor antagonist, in combination with paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer. *Clin Cancer Res* 2008; **14:** 1464–9.
9. Phuphanich S, *et al.* New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Phase I safety study of escalating doses of atrasentan in adults with recurrent malignant glioma. *Neuro-oncol* 2008; **10:** 617–623.

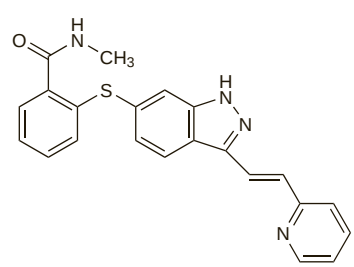
Axitinib *(USAN, rINN)*

AG-013736; Axitinibum. *N*-Methyl-2-({3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl}sulfanyl)benzamide.

Акситиниб

$C_{22}H_{18}N_4OS$ = 386.5.

CAS — 319460-85-0.



Profile

Axitinib is a tyrosine kinase inhibitor that is under investigation as an antineoplastic for the treatment of various cancers, including pancreatic, lung, gastrointestinal, and breast cancer, as well as melanoma.

◊ Reviews.

1. Sonpavde G, *et al.* Axitinib for renal cell carcinoma. *Expert Opin Invest Drugs* 2008; **17:** 741–8.
2. Choueiri TK. Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. *Curr Opin Investig Drugs* 2008; **9:** 658–71.

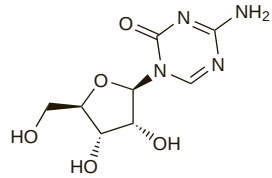
Azacitidine *(USAN, rINN)*

Azacitidina; 5-Azacitidina; Azacitidinum; 5-Azacytidine; Ladakamycin; NSC-102816; U-18496. 4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one.

Азацитидин

$C_8H_{12}N_4O_5$ = 244.2.

CAS — 320-67-2.



Adverse Effects and Precautions

The adverse effects of azacitidine are generally similar to those seen with cytarabine (p.705). Hypokalaemia, dyspnoea, and bruising are common.

Pharmacokinetics

Azacitidine is rapidly absorbed after subcutaneous use; the bioavailability relative to intravenous use is about 89%. The mean plasma half-life after subcutaneous injection is about 40 minutes. Azacitidine and its metabolites are excreted primarily in the urine; about 50% and 85% is recovered after subcutaneous and intravenous dosing, respectively. The mean elimination half-life is about 4 hours after subcutaneous or intravenous use.

◊ References.

1. Marcucci G, *et al.* Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. *J Clin Pharmacol* 2005; **45:** 597–602.
2. Tsao CF, *et al.* Azacitidine pharmacokinetics in an adolescent patient with renal compromise. *J Pediatr Hematol Oncol* 2007; **29:** 330–3.

Uses and Administration

Azacitidine is an antimetabolite antineoplastic with general properties similar to those of cytarabine (p.705). It also inhibits cellular pyrimidine synthesis. Azacitidine is used in myelodysplastic syndromes (p.654); it has also been used in the treatment of acute myeloid leukaemia (p.652).

For the treatment of myelodysplastic syndromes, azacitidine is given subcutaneously or intravenously in a dose of 75 mg/m^2 daily for 7 days, in 4-week cycles. If there is no benefit after 2 cycles, and no toxicity other than nausea and vomiting has occurred, the dose may be increased to 100 mg/m^2 daily. Treatment for at least 4 cycles is usually needed.

Azacitidine should be used with caution in renal impairment and doses adjusted accordingly (see below).

◊ References.

1. Anonymous. Azacitidine (Vidaza) for myelodysplastic syndrome. *Med Lett Drugs Ther* 2005; **47:** 11.
2. Sullivan M, *et al.* Azacitidine: a novel agent for myelodysplastic syndromes. *Am J Health-Syst Pharm* 2005; **62:** 1567–73.
3. Kuykendall JR. 5-Azacytidine and decitabine monotherapies of myelodysplastic disorders. *Ann Pharmacother* 2005; **39:** 1700–9.
4. Siddiqui MAA, Scott LJ. Azacitidine: in myelodysplastic syndromes. *Drugs* 2005; **65:** 1781–9.
5. Kaminskas E, *et al.* FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist* 2005; **10:** 176–82.
6. Silverman LR, *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.
7. Abdulhaq H, Rossetti JM. The role of azacitidine in the treatment of myelodysplastic syndromes. *Expert Opin Invest Drugs* 2007; **16:** 1967–75.
8. O'Dwyer K, Maslak P. Azacitidine and the beginnings of therapeutic epigenetic modulation. *Expert Opin Pharmacother* 2008; **9:** 1981–6.

Administration in renal impairment. Adverse renal effects of azacitidine include abnormalities in renal-function tests, renal tubular acidosis, renal failure, and death. US licensed product information recommends that if serum-bicarbonate concentrations fall to below 20 mEq/litre, the dose of azacitidine should be halved for the next course. If there are rises in serum concentrations of urea or creatinine, the next cycle of azacitidine should be delayed until these return to normal or baseline, and the dose should be halved on the next treatment course.

Preparations

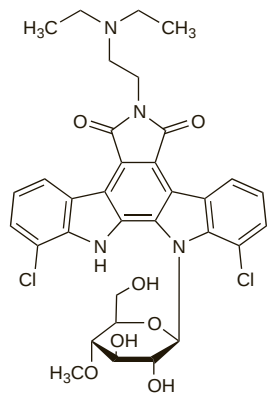
Proprietary Preparations (details are given in Part 3)
USA: Vidaza.

Becatecarin *(USAN, rINN)*

Becatecarina; Bécatécarine; Becatecarinum; BMS-181176; BMY-27557; NSC-655649; XL-119. 1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-*O*-methyl-β-D-glucopyranosyl)-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione.

Бекатекарин

$C_{33}H_{34}Cl_2N_4O_7$ = 669.6.
CAS — 119673-08-4.



Profile

Becatecarin is an antineoplastic under investigation in the treatment of bile-duct and other tumours.

◊ References.

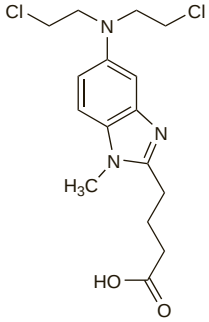
1. Merchant J, *et al.* Phase I clinical and pharmacokinetic study of NSC 655649, a rebeccamycin analogue, given in both single-dose and multiple-dose formats. *Clin Cancer Res* 2002; **8:** 2193–2201.
2. Goel S, *et al.* A phase II study of rebeccamycin analog NSC 655649 in patients with metastatic colorectal cancer. *Invest New Drugs* 2003; **21:** 103–7.
3. Langevin AM, *et al.* Phase I trial of rebeccamycin analog (NSC #655649) in children with refractory solid tumors: a pediatric oncology group study. *J Pediatr Hematol Oncol* 2003; **25:** 526–33.
4. Hussain M, *et al.* A phase II study of rebeccamycin analog (NSC-655649) in metastatic renal cell cancer. *Invest New Drugs* 2003; **21:** 465–71.
5. Ricart AD, *et al.* Phase I and pharmacokinetic study of sequences of the rebeccamycin analogue NSC 655649 and cisplatin in patients with advanced solid tumors. *Clin Cancer Res* 2005; **11:** 8728–36.
6. Langevin AM, *et al.* Children's Oncology Group. A phase II trial of rebeccamycin analogue (NSC #655649) in children with solid tumors: a Children's Oncology Group study. *Pediatr Blood Cancer* 2008; **50:** 577–80.

Bendamustine Hydrochloride *(USAN, rINNM)*

Bendamustine, Chlorhydrate de; Bendamustini Hydrochloridum; Hidrocloruro de bendamustina; IMET-3393; SDX-105. 5-[Bis(2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride.

Бендамустина Гидрохлорид

$C_{16}H_{21}Cl_2N_3O_2$, HCl = 394.7.
CAS — 16506-27-7 (bendamustine); 3543-75-7 (bendamustine hydrochloride).



(bendamustine)

Stability. US licensed product information for bendamustine hydrochloride states that, once reconstituted as directed and further diluted with sodium chloride 0.9%, the final infusion solution is stable for 24 hours when refrigerated (2° to 8°) or for 3 hours when stored at room temperature (15° to 30°) and exposed to light.

Adverse Effects, Treatment, and Precautions

Bendamustine commonly causes myelosuppression and doses may need to be reduced (see Uses and Administration, below); patients are therefore susceptible to infection. Other common adverse effects include gastrointestinal disturbances, fever, asthenia, fatigue, malaise, dry mouth, somnolence, cough, headache, mucosal inflammation, and stomatitis. Infusion reactions are common; symptoms include fever, chills, pruritus, and rash. Anaphylactic reactions have been reported rarely, especially during the second and subsequent cycles of therapy. Prophylactic antihistamines, antipyretics, and corticosteroids should be considered. If severe infusion reactions occur, stopping therapy should be considered. Tumour lysis syndrome has been reported, usually within the first treatment cycle, and may lead to acute renal failure and death. Adequate volume status should be maintained and potassium and uric acid concentrations should be monitored; allopurinol may be used in patients at high risk. Skin reactions such as bullous exanthema can occur with bendamustine; therapy may need to be withheld or stopped. Worsening hypertension, including hypertensive crisis, has also occurred. Increases in creatinine concentrations and liver enzyme values have been reported; bendamustine should be used with caution in patients with renal or hepatic impairment.

Interactions

Bendamustine is extensively metabolised by cytochrome P450 isoenzyme CYP1A2. Inhibitors of CYP1A2, such as fluvoxamine and ciprofloxacin, may increase exposure to bendamustine. Conversely, CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine; tobacco smoking also may increase exposure to bendamustine.

Pharmacokinetics

Bendamustine is about 95% bound to plasma proteins; data suggest it is not likely to displace nor to be displaced by highly protein-bound drugs. Bendamustine distributes freely into human red blood cells. It is mainly metabolised by hydrolysis via the cytochrome P450 isoenzyme CYP1A2. Little or no accumulation in plasma is anticipated for intravenous doses of bendamustine given on days 1 and 2 of a 28-day cycle. About 90% of the drug is eliminated, mainly via the faeces.

Uses and Administration

Bendamustine is an antineoplastic alkylating agent. It is given intravenously as the hydrochloride for the treatment of chronic lymphocytic leukaemia (p.653); it may also be used in non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and breast cancer.

For the treatment of chronic lymphocytic leukaemia, bendamustine hydrochloride is given in a dose of 100 mg/m^2, in 500 mL of sodium chloride 0.9%, infused over 30 minutes on days 1 and 2 of a 28-day cycle, for up to 6 cycles.

Doses are modified if toxicity occurs; dose delays may be warranted until neutrophils and platelets have recovered to acceptable concentrations. For severe haematological or non-haematological toxicity, doses should be reduced to 50 mg/m^2 on days 1 and 2 of each cycle. If severe haematological toxicity recurs, the dose should be further reduced to 25 mg/m^2. Dose re-escalation in subsequent cycles may be considered.

◊ References.

1. Barman Balfour JA, Goa KL. Bendamustine. *Drugs* 2001; **61:** 631–8.
2. Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. *Semin Oncol* 2002; **29** (4 suppl 13): 4–11.
3. Rummel MJ, *et al.* Bendamustine in the treatment of non-Hodgkin's lymphoma: results and future perspectives. *Semin Oncol* 2002; **29** (4 suppl 13): 27–32.
4. Rummel MJ, *et al.* Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol* 2005; **23:** 3383–9.
5. von Minckwitz G, *et al.* Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicenter trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. *Anticancer Drugs* 2005; **16:** 871–7.
6. Herold M, *et al.* Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma: results of a randomised phase III trial (OSHO 19). *J Cancer Res Clin Oncol* 2006; **132:** 105–12.
7. Ponisch W, *et al.* Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone—a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). *J Cancer Res Clin Oncol* 2006; **132:** 205–12.
8. Eichbaum MH, *et al.* Weekly administration of bendamustine as salvage therapy in metastatic breast cancer: final results of a phase II study. *Anticancer Drugs* 2007; **18:** 963–8.
9. Friedberg JW, *et al.* Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J Clin Oncol* 2008; **26:** 204–10. Correction. *ibid.*; 1911.
10. Apostolopoulos C, *et al.* Bendamustine as a model for the activity of alkylating agents. *Future Oncol* 2008; **4:** 323–32.

Administration in hepatic impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in mild hepatic impairment, data are limited, and therefore caution should be exercised when using bendamustine in these patients. Bendamustine should not be used in moderate or severe hepatic impairment due to a lack of data.

Administration in renal impairment. US licensed product information states that, although no meaningful effect on the pharmacokinetics of bendamustine was seen in renal impairment, data are limited, and therefore caution should be exercised in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with creatinine clearance less than 40 mL/minute, due to a lack of data.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Ribomustin; ***USA:*** Treanda.

Bevacizumab *(rINN)*

Bévacizumab; Bevacizumabum; rhuMAb-VEGF. Immunoglobulin G1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer.

Бевацизумаб

CAS — 216974-75-3.
ATC — L01XC07.
ATC Vet — QL01XC07.

Stability. UK licensed product information states that bevacizumab is chemically and physically stable for 48 hours at 2° to 30° in sodium chloride 0.9%, although immediate use is recommended from a microbiological point of view. If the solution is not used immediately, storage for longer than 24 hours at 2° to 8° cannot be recommended, unless dilution has taken place in controlled and validated aseptic conditions. In the USA, licensed product information states that bevacizumab solutions for infusion may be stored at 2° to 8° for up to 8 hours.

Bevacizumab should not be mixed with glucose.

Adverse Effects, Treatment, and Precautions

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

Bevacizumab may impair wound healing; therapy should not be started for at least 28 days after major surgery or until the surgical incision is fully healed; it should also be withheld before elective surgery. Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation is more common in patients receiving bevacizumab; fatalities have been reported. Bevacizumab should be stopped permanently in patients who develop gastrointestinal perforation, or fistulas, or wound dehiscence needing medical intervention. Very rare cases of nasal septum perforation have been reported.

Leucopenia, anaemia, neutropenia, thrombocytopenia, and febrile neutropenia have also occurred; severe neutropenia with infection has caused fatalities. Haemorrhage may occur; fatal pulmonary haemorrhage presenting as haemoptysis has been reported. There is an increased risk of serious thromboembolic events associated with the use of bevacizumab including stroke, transient ischaemic attacks, myocardial infarction, angina, and death. Bevacizumab may cause congestive heart failure; the risk is higher in those patients who have concurrent or previous treatment with anthracyclines. Hypertension, possibly dose-dependent, has occurred; blood pressure should be monitored, and therapy stopped in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria may develop; bevacizumab should be stopped in patients who develop nephrotic syndrome. Other adverse effects include asthenia, pain, abdominal pain, gastrointestinal disturbances, stomatitis, headache, epistaxis, dyspnoea, upper respiratory infection, and exfoliative dermatitis. Peripheral sensory neuropathy, syncope, somnolence, supraventricular tachycardia, palmar-plantar erythrodysesthesia syndrome, and muscular weakness have been commonly reported. Infusion reactions, manifesting as hypertension, wheezing, chest pain, headaches, rigors, and dia-