

Adrucil (fluorouracil)

Effective Date: 10/22/13

Date Developed: 9/3/13 by Albert Reeves MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20,
8/3/21, 2/1/22

Adrucil is an analog of pyrimidine and acts as an antineoplastic agent that interferes with DNA and RNA synthesis. Its metabolite (F-dUMP) inhibits thymidylate synthetase, thus depleting thymidine triphosphate (a necessary component of DNA synthesis)

Preauthorization Criteria: Treatment of breast cancer, colon cancer, rectal cancer, pancreatic cancer, and stomach (gastric) cancer

Off Label Uses: Anal cancer; Bladder cancer; Cervical cancer; Esophageal cancer; Head and neck cancer; Hepatobiliary cancers; Neuroendocrine tumors; Penile cancer (metastatic); Thymic cancers; Unknown primary cancer

NOTE: fluorouracil injection should be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

Dosing: refer to product literature for dosing for each specific disease and for renal or hepatic failure; is commonly used in combination with other chemotherapeutic agents for palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

How Supplied:

Adrucil: 500 mg/10 mL (10 mL); 2.5 g/50 mL (50 mL); 5 g/100 mL (100 mL)

Generic: 500 mg/10 mL (10 mL); 1 g/20 mL (20 mL); 2.5 g/50 mL (50 mL); 5 g/100 mL (100 mL)

Precautions: agranulocytosis; leukopenia; thrombocytopenia; CNS (cerebellar syndrome, altered mental status); Hand-foot syndrome; cardiovascular (arrhythmia, angina, acute MI, CVA)

Drug Interactions: strongly inhibits CYP2C9 and effects levels of those drugs metabolized by this cytochrome P450 enzyme (see product literature); enhances the immunosuppressant effect of

other medications.

References

1. Ajani JA, Moiseyenko VM, Tjulandin S, et al, "Quality of Life With Docetaxel Plus Cisplatin and Fluorouracil Compared With Cisplatin and Fluorouracil From a Phase III Trial for Advanced Gastric or Gastroesophageal Adenocarcinoma: The V-325 Study Group," *J Clin Oncol*, 2007, 25(22):3210-6.
2. Ajani JA, Winter KA, Gunderson LL, et al, "Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal: A Randomized Controlled Trial," *JAMA*, 2008, 299(16):1914-21.
3. Alberts SR, Al-Khatib H, Mahoney MR, et al, "Gemcitabine, 5-Fluorouracil, and Leucovorin in Advanced Biliary Tract and Gallbladder Carcinoma: A North Central Cancer Treatment Group Phase II Trial," *Cancer*, 2005, 103(1):111-8. [PubMed]
4. André T, Louvet C, Maindrault-Goebel F, et al, "CPT-11 (Irinotecan) Addition to Bimonthly, High-Dose Leucovorin and Bolus and Continuous-Infusion 5-Fluorouracil (FOLFIRI) for Pretreated Metastatic Colorectal Cancer. GERCOR," *Eur J Cancer*, 1999, 35(9):1343-7.
5. Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 100.
6. Assikis V, Buzdar A, Yang Y, et al, "A Phase III Trial of Sequential Adjuvant Chemotherapy for Operable Breast Carcinoma: Final Analysis With 10-Year Follow-Up," *Cancer*, 2003, 97(11):2716-23. Bamat MK, Tremmel R, O'Neil JD, et al, "Uridine Triacetate: An Orally Administered Life-Saving Antidote for 5-FU Overdose," *J Clin Oncol*, 28(15s):9084 [abstract 9084 from 2010 ASCO Annual Meeting].
7. Bang YJ, Van Cutsem E, Feyereislova A, et al, "Trastuzumab in Combination With Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Oesophageal Junction Cancer (ToGA): A Phase 3, Open-Label, Randomised Controlled Trial," *Lancet*, 2010, 376(9742):687-97.
8. Benaji B, Faouzi MA, Dine T, et al, "Compatibility Study of 5-Fluorouracil With PVC Bags After Repackaging Into Two Types of Infusion Admixtures," *Thérapie*, 1999, 54(5):659-63
9. Berry DL, Theriault RL, Holmes FA, et al, "Management of Breast Cancer During Pregnancy Using a Standardized Protocol," *J Clin Oncol*, 1999, 17(3):855-61.
10. Bourhis J, Sire C, Graff P, et al, "Concomitant Chemoradiotherapy versus Acceleration of Radiotherapy With or Without Concomitant Chemotherapy in Locally Advanced Head and Neck Carcinoma (GORTEC 99-02): An Open-Label Phase 3 Randomised Trial," *Lancet Oncol*, 2012, 13(2):145-53.
11. Buzdar AU, Kau SW, Smith TL, et al, "Ten-Year Results of FAC Adjuvant Chemotherapy Trial in Breast Cancer," *Am J Clin Oncol*, 1989, 12(2):123-8. [PubMed 2705401]
12. Cheeseman SL, Joel SP, Chester JD, et al, "A 'Modified de Gramont' Regimen of Fluorouracil, Alone and With Oxaliplatin, for Advanced Colorectal Cancer," *Br J Cancer*, 2002, 87(4):393-9.
13. Conroy T, Desseigne F, Ychou M, et al, "FOLFIRINOX Versus Gemcitabine for Metastatic Pancreatic Cancer," *N Engl J Med*, 2011, 364(19):1817-25
14. Cunningham D, Allum WH, Stenning SP, et al, "Perioperative Chemotherapy Versus Surgery Alone for Resectable Gastroesophageal Cancer," *N Engl J Med*, 2006, 355(1):11-20. [PubMed 16822992]
15. Denis F, Garaud P, Bardet E, et al, "Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma," *J Clin Oncol*, 2004, 22(1):69-76. [PubMed 14657228]



16. Diasio RB and Johnson MR, "The Role of Pharmacogenetics and Pharmacogenomics in Cancer Chemotherapy With 5-Fluorouracil," *Pharmacology*, 2000, 61(3):199-203. [PubMed 10971206]
17. Dowell JE, Garrett AM, Shyr Y, et al, "A Randomized Phase II Trial in Patients With Carcinoma of an Unknown Primary Site," *Cancer*, 2001, 91(3):592-7. [PubMed 11169943]
18. Eifel PJ, Winter K, Morris M, et al, "Pelvic Irradiation With Concurrent Chemotherapy versus Pelvic and Para-Aortic Irradiation for High-Risk Cervical Cancer: An Update of Radiation Therapy Oncology Group Trial (RTOG) 90-01," *J Clin Oncol*, 2004, 22(5):872-80. [PubMed 14990643]
19. Floyd J, Mirza I, Sachs B, et al, "Hepatotoxicity of Chemotherapy," *Semin Oncol*, 2006, 33(1):50-67. [PubMed 16473644]
20. Floyd JD, Nguyen DT, Lobins RL, et al, "Cardiotoxicity of Cancer Therapy," *J Clin Oncol*, 2005, 23(30):7685-96. [PubMed 16234530]
21. Forastiere AA, Metch B, Schuller DE, et al, "Randomized Comparison of Cisplatin Plus Fluorouracil and Carboplatin Plus Fluorouracil Versus Methotrexate in Advanced Squamous-Cell Carcinoma of the Head and Neck: A Southwest Oncology Group Study," *J Clin Oncol*, 1992, 10(8):1245-51. [PubMed 1634913]
22. Fournet A, Gilard V, Malet-Martino M, et al, "Stability of Commercial Solutions of 5-Fluorouracil for Continuous Infusion in an Ambulatory Pump," *Cancer Chemother Pharmacol*, 2000, 46(6):501-6. [PubMed 11138464]
23. Gibson MK, Li Y, Murphy B, et al, "Randomized Phase III Evaluation of Cisplatin Plus Fluorouracil Versus Cisplatin Plus Paclitaxel in Advanced Head and Neck Cancer (E1395): An Intergroup Trial of the Eastern Cooperative Oncology Group," *J Clin Oncol*, 2005, 23(15):3562-7. [PubMed 15908667]
24. Goldhirsch A, Colleoni M, Coates AS, et al, "Adding Adjuvant CMF Chemotherapy to Either Radiotherapy or Tamoxifen: Are All CMFs Alike? The International Breast Cancer Study Group (IBCSG)," *Ann Oncol*, 1998, 9(5):489-93. [PubMed 9653488]
25. Griggs JJ, Mangu PB, Anderson H, et al, "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," *J Clin Oncol*, 2012, 30(13):1553-61. [PubMed 22473167]
26. Gunderson LL, Winter KA, Ajani JA, et al, "Long-Term Update of US GI Intergroup RTOG 98-11 Phase III Trial for Anal Carcinoma: Survival, Relapse, and Colostomy Failure With Concurrent Chemoradiation Involving Fluorouracil/Mitomycin versus Fluorouracil/Cisplatin," *J Clin Oncol*, 2012, 30(35):4344-51. [PubMed 23150707]
27. Hahn KM, Johnson PH, Gordon N, et al, "Treatment of Pregnant Breast Cancer Patients and Outcomes of Children Exposed to Chemotherapy *In utero*," *Cancer*, 2006, 107(6):1219-26. [PubMed 16894524]
28. Haller DG, Catalano PJ, Macdonald JS, et al, "Phase III Study of Fluorouracil, Leucovorin, and Levamisole in High-Risk Stage II and III Colon Cancer: Final Report of Intergroup 0089," *J Clin Oncol*, 2005, 23(34):8671-8. [PubMed 16314627]
29. Hezel AF and Zhu AX, "Systemic Therapy for Biliary Tract Cancers," *Oncologist*, 2008, 13(4):415-23. [PubMed 18448556]
30. James ND, Hussain SA, Hall E, et al, "Radiotherapy With or Without Chemotherapy in Muscle-Invasive Bladder Cancer," *N Engl J Med*, 2012, 366(16):1477-88. [PubMed 22512481]
31. Janus N, Thariat J, Boulanger H, et al, "Proposal for Dosage Adjustment and Timing of Chemotherapy in Hemodialyzed Patients," *Ann Oncol*, 2010, 21(7):1395-403. [PubMed 20118214]
32. Koren G, Beatty K, Seto A, et al, "The Effects of Impaired Liver Function on the Elimination of Antineoplastic Agents," *Ann Pharmacother*, 1992, 26(3):363-71. [PubMed 1554959]
33. Kouvaraki MA, Ajani JA, Hoff P, et al, "Fluorouracil, Doxorubicin, and Streptozocin in the Treatment of Patients With Locally Advanced and Metastatic Pancreatic Endocrine Carcinomas," *J Clin Oncol*, 2004, 22(23):4762-71. [PubMed 15570077]
34. KueblerJP, Wieand HS, O'Connell MJ, et al, "Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin as Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07," *J Clin Oncol*, 2007, 25(16):2198-204. [PubMed 17470851]



35. Kusaba H, Shibata Y, Arita S, et al, "Infusional 5-Fluorouracil and Cisplatin as First-Line Chemotherapy in Patients With Carcinoma of Unknown Primary Site," *Med Oncol*, 2007, 24(2):259- 64. [PubMed 17848753]
36. Levine MN, Bramwell VH, Pritchard KI, et al, "Randomized Trial of Intensive Cyclophosphamide, Epirubicin, and Fluorouracil Chemotherapy Compared With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer, National Cancer Institute of Canada Clinical Trials Group," *J Clin Oncol*, 1998, 16(8):2651-8. [PubMed 9704715]
37. Martel P, Petit I, Pinguet F, et al, "Long-Term Stability of 5-Fluorouracil Stored in PVC Bags and in Ambulatory Pump Reservoirs," *J Pharm Biomed Anal*, 1996, 14(4):395-9. [PubMed 8729637]
38. Milano G and Chamorey AL, "Clinical Pharmacokinetics of 5-Fluorouracil With Consideration of Chronopharmacokinetics," *Chronobiol Int*, 2002, 19(1):177-89. [PubMed 11962674]
39. Morgan C, Tillett T, Braybrooke J, et al, "Management of Uncommon Chemotherapy-Induced Emergencies," *Lancet Oncol*, 2011, 12(8):806-14. [PubMed 21276754]
40. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™: Breast Cancer," Version 3.2012. Available at http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
41. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™: Esophageal and Esophagogastric Junction Cancers," Version 2.2012. Available at http://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf
42. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™: Gastric Cancer," Version 2.2012. Available at http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf
43. National Institute for Occupational Safety and Health (NIOSH), "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012." Available at <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>. Accessed January 21, 2013.
44. Neoptolemos JP, Stocken DD, Bassi C, et al, "Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid Vs Gemcitabine Following Pancreatic Cancer Resection: A Randomized Controlled Trial," *JAMA*, 2010, 304(10):1073-81. [PubMed 20823433]
45. Pelzer U, Schwaner I, Stieler J, et al, "Best Supportive Care (BSC) versus Oxaliplatin, Folinic Acid and 5-Fluorouracil (OFF) Plus BSC in Patients for Second-Line Advanced Pancreatic Cancer: A Phase III-Study From the German CONKO-Study Group," *Eur J Cancer*, 2011, 47(11):1676-81. [PubMed 21565490]
46. Posner MR, Hershock DM, Blajman CR, et al, "Cisplatin and Fluorouracil Alone or With Docetaxel in Head and Neck Cancer," *N Engl J Med*, 2007, 357(17):1705-15. [PubMed 17960013]
47. Regine WF, Winter KA, Abrams RA, et al, "Fluorouracil vs Gemcitabine Chemotherapy Before and After Fluorouracil-Based Chemoradiation Following Resection of Pancreatic Adenocarcinoma: A Randomized Controlled Trial," *JAMA*, 2008, 299(9):1019-26. [PubMed 18319412]
48. Schmitt J and Loehrer PJ Sr, "The Role of Chemotherapy in Advanced Thymoma," *J Thorac Oncol*, 2010, 5(10 Suppl 4):357-60. [PubMed 20859133]
49. Shamma FV, Ous S, and Fossa SD, "Cisplatin and 5-Fluorouracil in Advanced Cancer of the Penis," *J Urol*, 1992, 147(3):630-2. [PubMed 1538445]
50. Stiles ML, Allen LV, and Prince SJ, "Stability of Deferoxamine Mesylate, Floxuridine, Fluorouracil, Hydromorphone Hydrochloride, Lorazepam, and Midazolam Hydrochloride in Polypropylene Infusion-Pump Syringes," *Am J Health Syst Pharm*, 1996, 53(13):1583-8. [PubMed 8809281]
51. Sumpter K, Harper-Wynne C, Cunningham D, et al, "Report of Two Protocol Planned Interim Analyses in a Randomized Multicenter Phase III Study Comparing Capecitabine With Fluorouracil and Oxaliplatin With Cisplatin in Patients With Advanced Oesophagogastric Cancer Receiving ECF," *Br J Cancer*, 2005, 92(11):1976-83. [PubMed 15928658]
52. Tepper J, Krasna MJ, Niedzwiecki D, et al, "Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer:

- CALGB 9781," *J Clin Oncol*, 2008, 26(7):1086-92. [PubMed 18309943] Trissel LA, Martinez JF, and Xu QA, "Incompatibility of Fluorouracil With Leucovorin Calcium or Levoleucovorin Calcium," *Am J Health Syst Pharm*, 1995, 52(7):710-5. [PubMed 7627739]
53. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al, "Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group," *J Clin Oncol*, 2006, 24(31):4991-7. [PubMed 17075117]
54. Vermorken JB, Mesia R, Rivera F, et al, "Platinum-Based Chemotherapy Plus Cetuximab in Head and Neck Cancer," *N Engl J Med*, 2008, 359(11):1116-27. [PubMed 18784101]
55. Vermorken JB, Remenar E, van Herpen C, et al, "Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer," *N Engl J Med*, 2007, 357(17):1695-1704. [PubMed 17960012]
56. von Borstel R, O'Neil J, and Bamat M, "Vistonuridine: An Orally Administered, Life-Saving Antidote for 5-Fluorouracil (5FU) Overdose," *J Clin Oncol*, 2009, 27(15S):9616 [abstract 9616 from 2009 ASCO Annual Meeting]

Revision History:

Date Approved by P&T Committee: 10/22/13
 Date Reviewed/No Updates: 1/28/14 by C. Sanders MD
 Date Approved by P&T Committee: 1/28/14
 Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
 Date Approved by P&T Committee: 1/27/15
 Date Reviewed/Updated: 6/29/15 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/26/16
 Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/24/17
 Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/23/18
 Date Reviewed/No Updates: 1/22/19 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/22/19
 Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 2/18/20
 Date Reviewed/ Updated: 8/3/21 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 8/3/21
 Date Reviewed/No Updates: 2/1/22 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 2/1/22

Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/23/18	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/22/19	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
2/18/20	No	Howard Taekman, MD; Robert Sterling, MD	Annual review



VENTURA COUNTY
HEALTH CARE PLAN

8/3/21	Yes	Howard Taekman, MD; Robert Sterling, MD	Formatting changes
2/1/22	No	Howard Taekman, MD; Robert Sterling, MD	Annual review