

FARMACI CON USO CONSOLIDATO NEL TRATTAMENTO DELLE NEOPLASIE E PATOLOGIE EMATOLOGICHE PER INDICAZIONI ANCHE DIFFERENTI DA QUELLE PREVISTE DAL PROVVEDIMENTO DI AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

<i>Principio attivo</i>	<i>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</i>
<b>Basiliximab</b>	<p><b>Profilassi della “malattia del trapianto verso l’ospite”o Graft versus Host Disease (GVHD) in pazienti sottoposti a trapianto allogenico di cellule staminali ematopoietiche non manipolate da donatore familiare HLA aploidentico.</b></p> <p>Ji SQ, Chen HR, Wang HX et al. G-CSF-primed haploidentical marrow transplantation without ex vivo T cell depletivo: an excellent alternative for high-risk leukemia. Bone Marrow Transplantation 2002; 30:861-866. 2002</p> <p>Chen HR, Ji SQ, Wang HX et al. Humanized anti-CD25 monoclonal antibody for prophylaxis of graft-versus-host disease (GVHD) in haploidentical bone marrow transplantation without ex vivo T-cell depletivo. Exp Hematol 2003; 31:1019-1025.</p> <p>Ji SQ, Chen HR, Yan HX et al. Anti-CD25 monoclonal antibody (basiliximab) for prevention of graft-versus-host disease after haploidentical bone marrow transplantation for hematological malignancies. Bone Marrow Transplantation 2005; 36:349-354.2005</p> <p>Wang HX, Yan HM, Wang ZD et al. Haploidentical hematopoietic stem cell transplantation in hematologic malignancies with G-CSF mobilie bone marrow plus peripheral blood stem cells grafts without T cell depletivo: a single center report of 29 cases. Leukemia &amp; Lymphoma 2012; 53:654-659.</p> <p>Lu DP, Dong L, Wu T et al. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. Blood 2006; 107: 3065-73.</p> <p>Huang XJ, Chang YJ. Unmanipulated HLA-mismatched/haploidentical blood and marrow hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2011; 17:197-204.</p> <p>Anasetti C, Martin PJ, Storb R et al. Prophylaxis of graft-versus-host disease by administration of the murine anti-IL-2 receptor antibody 2A3. Bone Marrow Transplant 1991; :375-381.</p> <p>Kircher B, Lätzer K, Gastl G and Nachbaur D. Comparative in vitro study of the</p>

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	<p>immunomodulatory activity of humanized and chimeric anti-CD25 monoclonal antibodies. Clin Exp Immunol 2003; 134:426-430.</p> <p>Fang J, Hu C, Hong M et al. Prophylactic effects of interleukin-2 receptor antagonists against graft-versus-host disease following unrelated donor peripheral blood stem cell transplantation. Biol Blood Marrow transplant 2012; 18:754-762.</p> <p>Di Bartolomeo P, Santarone S, De Angelis G et al. Haploidentical, unmanipulated, G-CSF-primed bone marrow transplantation for patients with high-risk hematologic malignancies. Blood 2012; 121:849-857.</p> <p>Huang R, Tu S, Deng L, Kang Q, Song C, Li Y. Myeloablative haploidentical hematopoietic stem cell transplantation using basiliximab for graft-versus-host disease prophylaxis. Hematology. 2014 Oct 16. [Epub ahead of print]</p> <p>Wang Z, Zheng X, Yan H, Li D, Wang H. Good outcome of haploidentical hematopoietic SCT as a salvage therapy in children and adolescents with acquired severe aplastic anemia. Bone Marrow Transplant. 2014 Aug 18. doi: 10.1038/bmt.2014.187. [Epub ahead of print]</p> <p>Wang JZ, Liu KY, Xu LP, Liu DH, Han W, Chen H, Chen YH, Zhang XH, Zhao T, Wang Y, Huang XJ. Basiliximab for the treatment of steroid-refractory acute graft-versus-host disease after unmanipulated HLA-mismatched/haploidentical hematopoietic stem cell transplantation. Transplant Proc. 2011 Jun;43(5):1928-33.</p> <p>Kekre N and Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist. Blood 2014; 124(3): 334-343.</p> <p>William Arcese, Alessandra Picardi, Stella Santarone, Gottardo De Angelis, Raffaella Cerretti, Laura Cudillo, Elsa Pennese, Pasqua Bavaro, Paola Oliosio, Teresa Dentamaro, Luca Cupelli, Anna Chierichini, Antonella Ferrari, Andrea Mengarelli, Maria Cristina Tirindelli, Manuela Testi, Fabio Di Piazza, Paolo Di Bartolomeo. Haploidentical,G-CSF Primed, Unmanipulated Bone Marrow Transplantation for Patients with High-Risk Haematological Malignancies: An Update. Bone Marrow Transplant. 2014 (in press).</p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
<b>Bendamustina</b>	<p><b>Utilizzo nella Leucemia linfatica cronica (LLC) in ricaduta:</b></p> <ul style="list-style-type: none"> <li>- In prima linea: in pazienti candidabili a schema immuno chemioterapico includente anticorpi monoclonali ma nei quali non è consigliata l'associazione chemioterapica fludarabina e ciclofosfamide;</li> <li>- Linea successiva alla I°: come monoterapia o in associazione a chemioterapia e/o anticorpi monoclonali:</li> </ul> <p>Kath R, Blumenstengel K, Fricke HJ, Höffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. J Cancer Res Clin Oncol. 2001;127:48-54.</p> <p>Bergmann MA, Goebeler ME, Herold M, et al. Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica. 2005 Oct;90(10):1357-64.</p> <p>Fischer K, Cramer P, Busch R, Stilgenbauer S, Bahlo J, Schweighofer CD, Böttcher S, Staib P, Kiehl M, Eckart MJ, Kranz G, Goede V, Elter T, Bühler A, Winkler D, Kneba M, Döhner H, Eichhorst BF, Hallek M, Wendtner CM. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011 Sep 10;29(26):3559-66.</p> <p>Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209–16.</p> <p><b>Utilizzo in monoterapia o in associazione ad anticorpi monoclonali nei linfomi non-Hodgkin indolenti in recidiva e nei linfomi mantellari in recidiva:</b></p> <p>Heider A, Niederle N. Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas. Anticancer Drugs. 2001 Oct;12(9):725-9.</p> <p>Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2002 Aug;13(8):1285-9.</p>

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	<p>Friedberg JW, Cohen P, Chen L, 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 Jan 10;26(2):204-10.</p> <p>Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008 Sep 20;26(27):4473-9.</p> <p>Kahl BS, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, Czuczman MS, Robinson KS, Joyce R, van der Jagt RH, Cheson BD. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer. 2010 Jan 1;116(1):106-14.</p> <p>Ohmachi K, Ando K, Ogura M, Uchida T, Itoh K, Kubota N, et al., Japanese Bendamustine Lymphoma Study Group. Multicenter phase II study of bendamustine for relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Cancer Sci 2010;101:2059–64.</p> <p>Friedberg JW, Vose JM, Kelly JL, Young F, Bernstein SH, Peterson D, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood 2011;117:2807–12</p> <p>Visco C, Zambello R, Paolini R, Finotto S, Zanotti R, Zaja F, et al. Rituximab, bendamustine and cytarabine (R-BAC) is a very active regimen in patients with mantle cell lymphoma not eligible for intensive chemotherapy or autologous transplant. Blood 2011;118:2677.</p> <p>Visco C, Finotto S, Zambello R, Paolini R, Menin A, Zanotti R, Zaja F, Semenzato G, Pizzolo G, D'Amore ES, Rodeghiero F. Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. J Clin Oncol. 2013 Apr 10;31(11):1442-9.</p> <p>García-Noblejas A, Martínez Chamorro C, et al. Bendamustine as salvage treatment for patients with relapsed or refractory mantle cell lymphoma patients: a retrospective study of the Spanish experience. Ann Hematol. 2014 Apr 30.</p> <p><b>Utilizzo in pazienti con Linfoma di Hodgkin pretrattati con almeno due linee</b></p>

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	<p><b>chemioterapiche:</b>            Corazzelli G, Angrilli F, D’Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. Br J Haematol 2013;160(2):207–15.            Moskowitz AJ, Hamlin P, Gerecitano J, et al. Updated results of a phase II trial of bendamustine in relapsed and refractory Hodgkin lymphoma [abstract 288]. Ann Oncol 2011;22(suppl 4).</p> <p><b>Trattamento di prima linea dei linfomi indolenti a cellule B, in associazione a rituximab (originatore o biosimilare).</b>  <b>Trattamento di prima linea dei linfomi mantellari, limitatamente ai pazienti di età &gt; 65 anni, in associazione a rituximab (originatore o biosimilare).</b>            Rummel et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013 Apr 6;381(9873):1203-10.</p> <p><b>In monoterapia oppure in associazione a bortezomib e steroide, nel trattamento del mieloma multiplo recidivato e per il quale altri trattamenti sono inappropriati o controindicati.</b>            - Poenisch W et al, J Cancer Res Clin Oncol. 2012 Aug;138(8):1405-12            - Damaj G. et al. Leuk Lymphoma 2012 Apr; 53(4):632-4            - Poenisch W et al, J Cancer Res Clin Oncol. 2013 Mar;139(3):499-508            - Offidani M et al. Blood Cancer J. 2013 Nov 22; 3:e162            - Ludwig et al. Blood. 2014 Feb 13;123 (7):985-91</p>
<b>Bleomicina</b>	<p><b>Utilizzo in regimi di associazione (ABVD o simili) nel trattamento del linfoma di Hodgkin:</b>            Linee Guida NCCN 2006</p>
<b>Bortezomib</b>	<p><b>Utilizzo nel trattamento, con o senza rituximab (originatore o biosimilare), del linfoma mantellare recidivato.</b>            O’Connor OA, Wright J, Mosckowitz C, et al. Phase II clinical experience with the novel peptase inhibitor bortezomib in patient with indolent non Hodgkin lymphoma and</p>

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	<p>mantle cell lymphoma. J Clin Oncol. 2005; 23(4): 676-84</p> <p>Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non – Hodgkin’s lymphoma. J Clin Oncol. 2005; 23(4): 667-75</p> <p>Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006; 24: 4867-74</p> <p>Agathocleus A, Rohatiner A, Rule S, et al. Weekly versus twice weekly bortezomib given in conjunction with rituximab, in patients with recurrent follicular lymphoma, mantle cell lymphoma and Waldenstrom macroglobulinemia. Br J Haematol. 2010 (Epub ahead of print).</p> <p>Chiappella A, Pregno P, Zinzani PL, et al. The combination of bortezomib and rituximab is safe in relapsed and refractory indolent non follicular and mantle cell non hodgkin lymphoma: a phase II multicenter study by Intergruppo Italiano Linfomi. Blood 2009 (50th ASH annual meeting) 3758°</p> <p><b>Utilizzo in monoterapia o in associazione a steroide e/o rituximab (originatore o biosimilare) per i pazienti affetti da macroglobulinemia di Waldenstrom in seconda o successiva linea di trattamento:</b></p> <p>Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or refractory Waldenstrom macroglobulinemia. J Clin Oncol. 2010; 28(8): 1422-8</p> <p>Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone and rituximab: WMCTG clinical trial 05-180. J Clin Oncol. 2009; 27(23): 3830-5</p> <p>Ghobrial IM, Xie W, , Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab untreated patients with Waldenstrom macroglobulinemia. Am J Hematol. 2010; 85(9): 670-4</p> <p><b>Utilizzo in prima linea dell’amiloidosi:</b></p> <p>Kastritis E, et al. Treatment of light chain (AL) amyloidosis with the combination of Bortezomib</p>

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	<p>and Dexamethasone. Haematologica. 2007;92:1351-1358.                      Kastritis E, et al. Bortezomib with and without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol. 2010;28:1031-1037.                      Wechaleker A, et al. Efficacy of Bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica. 2008;93:295-298.                      Reece D, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase I dose escalation study. Blood. 2009;114:1489-1497.</p> <p><b>Somministrazione settimanale, in associazione con melfalan e prednisone per il trattamento di pazienti adulti con mieloma multiplo non-pretrattati, non eleggibili a chemioterapia ad alte dosi con trapianto di cellule staminali ematopoietiche</b></p> <p><u>Takezako N. et al</u>, <i>Efficacy and Safety of Weekly Bortezomib Containing VMP Followed By Bortezomib Maintenance Therapy in Unfit or Frail Multiple Myeloma Patients</i>. Clin Lymphoma Myeloma Leuk 2017- 16<sup>th</sup> International Myeloma Workshop.</p> <p><u>Palumbo A. et al</u>, <i>Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial</i>. J Clin Oncol 2010.</p> <p><u>Palumbo A. et al</u>, <i>Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival</i>. J Clin Oncol 2014.</p>
<b>Busulfano</b>	<p><b>Utilizzato ad alte dosi, da solo o in associazione, in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche</b></p> <p>Blaise D. et al., Blood 1992                      Clift R.A. et al., Blood 1994</p>
<b>Carboplatino</b>	<p><b>Utilizzato, in sostituzione del cisplatino, in regimi di associazione nel trattamento di</b></p>

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	<p><b>salvataggio dei linfomi maligni (Hodgkin e non-Hodgkin). Utilizzato ad alte dosi in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b>                      Ahmed T. et al., Leukemia 1994                      Demirer T. et al., Bone Marrow Transpl. 2004</p>
<b>Ciclofosfamide</b>	<p><b>Utilizzato ad alte dosi, da solo o in associazione, in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche, ed in protocolli di mobilizzazione dei progenitori emopoietici.</b>                      Blaise D. et al., Blood 1992                      Clift R.A. et al., Blood 1994                      Koc O.N. et al., J. Clin. Oncol. 2000</p>
<b>Ciclosporina</b>	<p><b>Utilizzo nell'anemia aplastica, malattie autoimmuni gravi, sindrome emofagocitica.</b>                      Walton RC, Onciu MM. Am J Ophthalmol. 2007 J                      Kennedy-Nasser AA, Biol Blood Marrow Transplant. 2006                      Acott PD, Transplant Proc. 2006.                      Kobayashi R, Br J Haematol. 2006                      Pattaragarn A, Pediatr Transplant. 2006</p>
<b>Cisplatino</b>	<p><b>Utilizzato in regimi di associazione nel trattamento di salvataggio dei linfomi maligni (Hodgkin e non-Hodgkin).</b>                      Cabanillas F. et al., Semin. Hematol. 1988</p>
<b>Citarabina</b>	<p><b>Utilizzato ad alte dosi, da solo o in associazione, nel trattamento delle leucemie acute, dei linfomi non-Hodgkin, ed in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b>                      Buchner T., Curr. Opin. Oncol. 1997                      Tarella C. et al., Ann. Hematol. 2001                      Linee Guida NCCN 2006</p>



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<b>Cladribina</b>	<p><b>Utilizzato, anche per via sottocutanea, da solo o in regimi di combinazione, nel trattamento di prima linea o di salvataggio delle malattie linfoproliferative croniche e dei linfomi non-Hodgkin indolenti.</b>            Blum KA et al, Cancer 2006            Robak T, Cancer Treat. Rev. 2007</p> <p><b>Trattamento dell'istiocitosi a cellule di Langerhans. Uso sottocutaneo.</b>            Donadieu J, Bernard F, van Noesel M, Barkaoui M, Bardet O, Mura R, Arico M, Piguet C, Gandemer V, Armari Alla C, Clausen N, Jeziorski E, Lambilliotte A, Weitzman S, Henter JI, Van Den Bos C; Salvage Group of the Histiocyte Society. Cladribine and cytarabine in refractory multisystem Langerhans cell histiocytosis: results of an international phase 2 study. Blood. 2015 Sep 17;126(12):1415-1423.            Gadner H, Minkov M, Grois N, Pötschger U, Thiem E, Aricò M, Astigarraga I, Braier J, Donadieu J, Henter JI, Janka-Schaub G, McClain KL, Weitzman S, Windebank K, Ladisch S; Histiocyte Society. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013 Jun 20;121(25):5006-14.            Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, Egeler RM, Janka G, Micic D, Rodriguez-Galindo C, Van Gool S, Visser J, Weitzman S, Donadieu J; Euro Histo Network. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013 Feb;60(2):175-84.            Adam Z, Szturz P, Vaníček J, Moulis M, Pour L, Krejčí M, et al. Cladribine (2 chlorodeoxyadenosine) in frontline chemotherapy for adult Langerhans cell histiocytosis: A single-center study of seven cases. Acta Oncol. 2013.            Weitzman S, Braier J, Donadieu J, Egeler RM, Grois N, Ladisch S, et al. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). Results of the LCH-S-98 protocol of the Histiocyte Society. Pediatr Blood Cancer 2009;53(7):1271-6.            Apollonsky N, Lipton JM. Treatment of refractory Langerhans cell histiocytosis (LCH) with a combination of 2-chlorodeoxyadenosine and cytosine arabinoside. J Pediatr Hematol Oncol 2009;31(1):53-6.</p>

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	<p>Gadner H, Grois N, Pötschger U, Minkov M, Aricò M, Braier J, Broadbent V, Donadieu J, Henter JI, McCarter R, Ladisch S; Histiocyte Society. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood. 2008 Mar 1;111(5):2556-62.</p> <p>Bernard F, Thomas C, Bertrand Y, Munzer M, Landman Parker J, Ouache M, et al. Multi-centre pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. Eur J Cancer 2005;41(17):2682-9.</p> <p>Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, Komp D, Michaelis J, Nicholson S, Pötschger U, Pritchard J, Ladisch S; Histiocyte Society. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr. 2001 May;138(5):728-34.</p> <p>Saven A, Burian C. Cladribine activity in adult Langerhans-cell histiocytosis. Blood 1999;93(12):4125-30.</p>
<b>Concentrati di FVIII e FIX</b>	<p><b>Induzione della tolleranza immunologica in pazienti affetti da emofilia A o B congenita con anticorpi inibitori.</b></p> <p>-The hemophilias--from royal genes to gene therapy. Mannucci PM, Tuddenham EG. N Engl J Med, 344,1773-1999 (2001).</p> <p>-Immune tolerance in hemophilia with factor VIII inhibitors: predictors of success. Mariani G, Kroner B; Immune Tolerance Study Group (ITSG). Haematologica, 86,1186-93 (2001).</p> <p>-The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. DiMichele DM, Kroner BL; North American Immune Tolerance Study Group. Thromb Haemost,87,52-57 (2002).</p> <p>-The principal results of the International Immune Tolerance Study: a randomized dose comparison. Hay CR, DiMichele DM; International Immune Tolerance Study Blood, 119,1335-1344 (2012).</p>
<b>Doxorubicina</b>	<p><b>Utilizzato in regimi di associazione (VAD o simili) nel trattamento del mieloma multiplo.</b></p> <p>Linee Guida SIE 2004</p>

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<b>Doxorubicina liposomiale (Myocet)</b>	<p><b>In associazione a ciclofosfamide, vincristina, prednisone e rituximab (originatore o biosimilare) in pazienti affetti da linfoma non Hodgkin aggressivo, con associata cardiopatia o pretrattati con antracicline o anziani.</b></p> <p>Rigacci L. et al. Liposome-encapsulated doxorubicin in combination with cyclofosfamide, vincristine, prednisone and rituximab in patients with lymphoma and concurrent cardiac diseases or pre-treated with antracyclines, Hematol Oncol. 2007 Dec;25(4):198-203.</p> <p>Federico M. et al. An international, open-label Phase II study of cyclophosphamide, vincristine, non-pegylated liposomal doxorubicin (Myocet), and prednisone with rituximab (R-COMP chemoimmunotherapy) in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma, 11<sup>th</sup> Congress of the European Hematology Association 2006.</p> <p><b>In associazione a ciclofosfamide, vincristina, prednisone in pazienti affetti da linfoma non Hodgkin aggressivo a cellule T, con associata cardiopatia o pretrattati con antracicline o anziani.</b></p> <p>Tulpule A. et al. Phase I/II Trial of Nonpegylated liposomal doxorubicin, cyclophosphamide, vincristine and prednisone in the treatment of newly diagnosed aggressive non-hodgkin's lymphoma, Clinical Lymphoma and Myeloma 2006 vol.7 No.1 59-64.</p>
<b>Epoetina alfa</b>	<p><b>Utilizzo nel trattamento dell'anemia (Hgb &lt; 10 g/dL o riduzione dell'emoglobina &gt; 2 g/dL durante un qualsiasi periodo di 4 settimane di trattamento) nei pazienti per il trattamento dell'infezione cronica da HCV e che presentano risposta virologica alla terapia.</b></p> <p>N.Bräu, Journal of viral Hepatitis, 2004, 11, 191-197</p> <p>Dieterich DT, Am J Gastroenterol. 2003 Nov; 98 (11): 2491-9</p> <p>Shiffman ML, Hepatology. 2007 Aug; 46 (2): 371-9</p> <p>Homoncik M., Am J Gastroenterol. 2006 Oct; 101(10): 2275-82.</p> <p>Sharvadze L, Georgian Med News. 2006 Aug; (137): 62-5</p>

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	<p>Jain A, Transplant Proc. 2005 Sep; 37 (7): 3190-6                      Abonyi ME, Anticancer Res. 2005 Mar-Apr; 25 (2B): 1315-20                      Balan V, Am J Gastroenterol. 2005 Feb; 100(2): 299-307.                      Shergill AK, Am J Transplant. 2005 Jan; 5 (1): 118-24                      Pockros PJ, Hepatology. 2004 Dec;40 (6): 1450-8                      Afdhal NH, Gastroenterology. 2004 May; 126(5): 1302-11                      Lunel-Fabiani F, Pathol Biol (Paris). 2003 Oct; 51 (8-9): 520-4                      Gergely AE, Hepatology. 2002 May;35 (5): 1281-2                      Talal AH, Am J Gastroenterol. 2001 Sep; 96(9): 2802-4.</p> <p><b>In pazienti HIV pluritrattati con anemia (Hgb &lt; 8,5 g/dL) nei quali l'uso di farmaci anemizzanti è l'unica alternativa terapeutica.</b></p> <p>Pau AK, AIDS Care SRDS. 2006 Sep;20 (9): 612-9                      Alvarez D, J Viral Hepat. 2006 Oct; 13 (10): 683-9                      Sulkowski MS, J Acquir Immune Defic Syndr. 2005 Aug 1; 39 (4): 504-6</p>
<b>Epoetina beta</b>	<p><b>Trattamento dell'anemia (Hgb &lt; 10 g/dL o riduzione dell'emoglobina &gt; 2 g/dL durante un qualsiasi periodo di 4 settimane di trattamento) nei pazienti per il trattamento dell'infezione cronica da HCV e che presentano risposta virologica alla terapia.</b></p> <p>N.Bräu, Journal of viral Hepatitis, 2004, 11, 191-197                      Dieterich DT, Am J Gastroenterol. 2003 Nov; 98 (11): 2491-9                      Shiffman ML, Hepatology. 2007 Aug; 46 (2): 371-9                      Homoncik M., Am J Gastroenterol. 2006 Oct; 101(10): 2275-82.                      Sharvadze L, Georgian Med News. 2006 Aug; (137): 62-5                      Jain A, Transplant Proc. 2005 Sep; 37 (7): 3190-6                      Abonyi ME, Anticancer Res. 2005 Mar-Apr; 25 (2B): 1315-20                      Balan V, Am J Gastroenterol. 2005 Feb; 100(2): 299-307.                      Shergill AK, Am J Transplant. 2005 Jan; 5 (1): 118-24                      Pockros PJ, Hepatology. 2004 Dec;40 (6): 1450-8</p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	<p>Afdhal NH, Gastroenterology. 2004 May; 126(5): 1302-11                      Lunel-Fabiani F, Pathol Biol (Paris). 2003 Oct; 51 (8-9): 520-4                      Gergely AE, Hepatology. 2002 May;35 (5): 1281-2                      Talal AH, Am J Gastroenterol. 2001 Sep; 96(9): 2802-4.</p> <p><b>In pazienti HIV pluritrattati con anemia (Hgb &lt; 8,5 g/dL) nei quali l'uso di farmaci anemizzanti è l'unica alternativa terapeutica.</b></p> <p>Pau AK, AIDS Care SRDS. 2006 Sep;20 (9): 612-9                      Alvarez D, J Viral Hepat. 2006 Oct; 13 (10): 683-9                      Sulkowski MS, J Acquir Immune Defic Syndr. 2005 Aug 1; 39 (4): 504-6</p>
<b>Etoposide</b>	<p><b>Utilizzato in regimi di associazione nel trattamento della leucemia linfoide acuta e del mieloma multiplo.</b></p> <p><b>Utilizzato ad alte dosi, da solo o in associazione, in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b></p> <p>Linker C. et al., J. Clin. Oncol. 2002                      Cogle C.R. et al., Am. J. Hematol. 2003                      Linee Guida SIE 2004</p>
<b>Fibrinogeno (Riastap)</b>	<p><b>Trattamento delle diatesi emorragiche da carenza di fibrinogeno acquisita.</b></p>
<b>Fludarabina</b>	<p><b>Utilizzato in regimi di associazione nel trattamento dei linfomi non-Hodgkin, delle leucemie acute, della leucemia linfatica cronica ed in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b></p> <p>Zinzani P.L., Best Pract. Res. Clin. Haematol. 2002                      Virchis A. et al., Br. J. Haematol. 2004                      Foss F.M., Semin. Hematol. 2006</p>
<b>Gemcitabina</b>	<p><b>Utilizzato, da solo o in regimi di associazione, nel trattamento del linfoma di Hodgkin e dei linfomi non-Hodgkin.</b></p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	Chau L. et al., Clin. Lymphoma 2002 Bredenfeld H. et al., J. Clin. Oncol. 2004
<b>Idrossiurea (idrossicarbamide)</b>	<b>Utilizzo nel trattamento di citoriduzione della leucemia mieloide acuta.</b> Sekeris M.A., Stone R.M., Curr. Opin. Oncol. 2002 Linee Guida NCCN 2006
<b>Ifosfamide</b>	<b>Utilizzo in regimi di associazione nel trattamento di salvataggio del linfoma di Hodgkin, ed in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b> Zinzani P.L. et al., Haematologica 1994 Oblon D.J. et al., Bone Marrow Transpl. 1997
<b>Interferone alfa 2a e 2b Peginterferone alfa 2a</b>	<b>Utilizzo come terapia di prima linea della trombocitopenia essenziale in gravidanza, ed in pazienti di età minore di 40 anni. Utilizzato come terapia di seconda linea della trombocitopenia essenziale in pazienti di età compresa tra 40-60 anni a basso rischio di complicanze tromboemboliche.</b> -Barbui T et al. J Clin Oncol. 2011 Feb 20;29(6):761-70. -Linee guida SIE, SIES, GITMO Haematologica. 2004 Feb;89(2):215-32.
<b>Lenalidomide</b>	<b>Utilizzo nei Linfomi diffusi a grandi cellule B recidivati-refrattari a precedenti trattamenti chemioterapici per i quali non si ravvisano alternative terapeutiche e non candidabili a trapianto di cellule staminali autologhe o allogeniche. Monitoraggio tramite Registro</b> <u>Witzig TE, et al. Results from a phase of lenalidomide oral monotherapy in relapsed/refractory indolent non Hodgkin's lymphoma.</u> Blood 2007 (49 ASH Annual Meeting) 2560 a <u>Vose JM, et al. High response rate to lenalidomide in relapsed/refractory aggressive non Hodgkin's lymphoma with prior stem cell transplant.</u> Blood 2007 (49 ASH Annual Meeting) 2570 a <u>Wiernik PH, et al. Lenalidomide monotherapy in relapsed refractory aggressive non Hodgkin's lymphoma.</u> J Clin Oncol. 2008; 26: 4952-7

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	<p><b>Utilizzo nell'amiloidosi in pazienti già trattati con melphalan e bortezomib (o in quelli che hanno controindicazioni a essere esposti a melphalan e/o bortezomib). Monitoraggio tramite Registro.</b></p> <p>Dispenzieri A, Lacy M, Zeldenrust S, et al: The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 109:465-470, 2007</p> <p>Sancharawala V, Wright D, Rosenzweig M, et al: Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 109:492-496, 2007</p> <p>Moreau P, Jaccard A, Benboubker L, et al: Lenalidomide in combination with melphalan and dexamethasone in patients with newly-diagnosed AL amyloidosis: a multicenter phase 1/2 dose escalation study. Blood, 2010</p> <p>Palladini G, Perfetti V, Obici L, et al: Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 103:2936-2938, 2004</p> <p>Jaccard A, Moreau P, Leblond V, et al: High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 357:1083-1093, 2007</p> <p>Specter R, Sancharawala V, Seldin D, et al: Kidney dysfunction during lenalidomide treatment for AL amyloidosis. Nephrol Dial Transplant, 2010 (in press)</p> <p>Palladini G, Russo P, Bragotti L, et al: A Phase II Trial of Cyclophosphamide, Lenalidomide and Dexamethasone (CLD) in Previously Treated Patients with AL Amyloidosis. Blood:1117-1118, 2009.</p>
<b>Melfalan</b>	<p><b>Utilizzato ad alte dosi, da solo o in associazione, in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche nei linfomi maligni e nelle leucemie acute e croniche.</b></p> <p>Singhal S. et al., Bone Marrow Transpl. 1996</p> <p>Giralt S. et al., Blood 2001</p>
<b>Metotrexate</b>	<p><b>Utilizzato ad alte dosi, da solo o in associazione, nel trattamento delle leucemie acute e dei linfomi non-Hodgkin. Utilizzato, in associazione con ciclosporina, nella profilassi della GVHD</b></p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	<p><b>in pazienti sottoposti ad allotrapianto di cellule staminali emopoietiche.</b>                      Gianni M. et al., N. Engl. J. Med. 1997                      Storb R. et al., N. Engl. J. Med. 1986                      Kantarjian H. et al., Cancer 2004                      Linee Guida NCCN 2006</p>
<b>Mitoxantrone</b>	<p><b>Utilizzato in regimi di associazione nel trattamento della leucemia linfoide acuta e cronica, nel linfoma di Hodgkin e non Hodgkin, nel mieloma multiplo, ed in regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b>                      Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, Ancliff P, Morgan M, Masurekar A, Goulden N, Green N, Révész T, Darbyshire P, Love S, Saha V. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010 Dec 11;376(9757):2009-17                      Weiss et al. JCO September 1996 vol. 14 no. 9 2480-2485                      Bosch F, Ferrer A, Villamor N, González M, Briones J, González-Barca E, Abella E, Gardella S, Escoda L, Pérez-Ceballos E, Asensi A, Sayas MJ, Font L, Altés A, Muntañola A, Bertazzoni P, Rozman M, Aymerich M, Giné E, Montserrat E. Fludarabine, cyclophosphamide, and mitoxantrone as initial therapy of chronic lymphocytic leukemia: high response rate and disease eradication. Clin Cancer Res. 2008 Jan 1;14(1):155-61. doi: 10.1158/1078-0432.CCR-07-1371.                      Köppler H, Fuss H, Hurtz HJ, Knigge O, Losem C, Reschke D, Schmitz S, Weide R, Weiß J, Hallek M; GCLLSG. Bendamustine plus mitoxantrone for relapsed/refractory chronic lymphocytic leukaemia (CLL): results of a multicentre phase II study of the German CLL Study Group (GCLLSG). Br J Haematol. 2012 Jul;158(2):238-41.                      McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Semin Oncol 2000;27:37-41.                      Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate</p>



<b>Principio attivo</b>	<b><i>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</i></b>
	<p>and prolongs survival as compared to FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas - results of a prospective randomized study of the German low grade lymphoma study group (GLSG). Blood 2004;104:3064-3071.</p> <p>Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003-4008.</p> <p>Ibrahim D, Smith MR, Varterasian M, Karanes C, Millenson M, Yeslow G, Pemberton P, Lai P, Abrams J, Al-Katib A. Phase II study of PEND chemotherapy in patients with refractory/relapsed Hodgkin lymphoma. Leuk Lymphoma. 2004 Oct;45(10):2079-84.</p> <p>Tarella C, Cuttica A, Vitolo U, Liberati M, Di Nicola M, Cortelazzo S, Rosato R, Rosanelli C, Di Renzo N, Musso M, Pavone E, Santini G, Pescarollo A, De Crescenzo A, Federico M, Gallamini A, Pregno P, Romano R, Coser P, Gallo E, Boccadoro M, Barbui T, Pileri A, Gianni AM, Levis A. High-dose sequential chemotherapy and peripheral blood progenitor cell autografting in patients with refractory and/or recurrent Hodgkin lymphoma: a multicenter study of the intergruppo Italiano Linfomi showing prolonged disease free survival in patients treated at first recurrence. Cancer. 2003 Jun 1;97(11):2748-59.</p> <p>Beaven AW, Moore DT, Sharf A, Serody JS, Shea TC, Gabriel DA. Infusional mitoxantrone plus bolus melphalan as a stem cell transplant conditioning regimen for multiple myeloma. Cancer Invest. 2011 Mar;29(3):214-9.</p> <p>Zinzani P.L.. et al., J. Clin. Oncol. 2004</p> <p>Buchner T.. et al., J. Clin. Oncol. 2003</p> <p>Tsimberidou A.M.. et al., Cancer 2004</p> <p>Linee Guida NCCN 2013</p>
<b>Oxaliplatino</b>	<b>Utilizzo nei schemi di salvataggio per LNH e LH con gemcitabina o ARA-C +/- rituximab (originatore o biosimilare)</b>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	<p>Machover D et al. Dexamethasone, high dose cytarabine and oxaliplatin (DHAOx) as salvage treatment for patients with initially refractory or relapsed non Hodgkin's lymphoma. (2001) Ann Oncol 12: 1439-43.</p> <p>Chau I et al. An oxaliplatino-based chemotherapy in patients with relapsed or refractory intermediate and high grade non-Hodgkin's lymphoma. (2001), Br J Haematol 115: 786-92.</p> <p>Sun Jin Sym et al. A multi center phase II trial of etoposide , methelprednisolone, hig dose cytarabine and oxaliplatin for patients with primary refractory/relapsed aggressive non Hodgkin's lymphoma. (2008) Cancer Chemoter Phatmacol.</p>
<b>Pentostatina</b>	<p><b>Utilizzato nel trattamento dei linfomi non-Hodgkin a cellule T. Utilizzato nella profilassi e nel trattamento della GVHD refrattaria a trattamenti di prima linea.</b></p> <p>Ho A.D. et al., Semin. Oncol. 2000</p> <p>Bolanos-Meade J. et al., J. Clin. Oncol. 2005</p> <p><b>Utilizzo, da solo o in regimi di associazione, nel trattamento di prima linea o di salvataggio della leucemia linfatica cronica.</b></p> <p>Dillman R.O., Expert Rev. Anticancer Ther. 2004</p> <p>Kay N.E. et al., Blood 2007</p>
<b>Plerixafor</b>	<p><b>Impiego in donatore di cellule staminali allogeniche familiare o da registro non mobilizzante.</b></p> <p>GITMO Procedura Operativa “ Gestione del donatore MUD di CSE periferiche non mobilizzante”  <a href="http://www.gitmo.it/images/pdf/segreteria/POA/SOPUDPASC.pdf">http://www.gitmo.it/images/pdf/segreteria/POA/SOPUDPASC.pdf</a></p> <p>Devine SM, et al. <i>Rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100, an antagonist of the CXCR4/SDF-1 interaction.</i> Blood 2008</p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	Gattillo S, et al. <i>Plerixafor on demand in ten healthy family donors as a rescue strategy to achieve an adequate graft for stem cell transplantation</i> . Transfusion 2015
<p><b>Rituximab*</b> <b>originatore o biosimilare</b></p> <p>*Per le modalità di somministrazione e relativa durata, fare riferimento all'RCP approvato in Italia o, in alternativa, alla scheda tecnica di Rituxan o Truxima approvate da FDA, con particolare attenzione alle eccezioni per i pazienti affetti da patologie cardiovascolari o con un numero di linfociti circolanti superiori a 5000/mm<sup>3</sup></p>	<p><b>Linfomi non-Hodgkin a cellule B (CD20 positivi), di qualunque istologia, in associazione con regimi vari di polichemioterapia (includenti farmaci quali antracicline, fludarabina, cisplatino, citarabina, etoposide, metotrexato) impiegati per il trattamento di prima linea o di salvataggio, inclusi i regimi di condizionamento pre-trapianto di cellule staminali emopoietiche.</b> Tarella C. et al., Cancer 2003 Linee Guida NCCN 2006</p> <p><b>Leucemia linfatica cronica a cellule B, in associazione con regimi di polichemioterapia (includenti antracicline, fludarabina) impiegati per il trattamento di prima linea o di salvataggio.</b> Keating M. et al., J. Clin. Oncol. 2005</p> <p><b>Profilassi e terapia dei disordini linfoproliferativi EBV-correlati in soggetti trapiantati (organi o cellule staminali emopoietiche).</b> Svoboda J. et al., Transpl. Int. 2006</p> <p><b>Terapia della GVHD acuta e cronica steroido-resistente.</b> Cutler C. et al., Blood 2006</p> <p><b>Utilizzo in monochemioterapia nei linfomi follicolari nei pazienti non candidabili al trattamento chemioterapico:</b> Martinelli et al., 2010 Journal of Clinical Oncology</p> <p><b>Linfomi di Hodgkin a predominanza linfocitaria in monoterapia e in associazione a</b></p>

<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
	<p><b>chemioterapia e in 1° linea e come terapia di salvataggio e di mantenimento:</b></p> <p>Nogova L, Reineke T, Brilliant C, Sieniawski M, Rudiger T, Josting A, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol. 2008 Jan 20;26(3):434-9.</p> <p>Jackson C, Sirohi B, Cunningham D, Horwich A, Thomas K, Wotherspoon A. Lymphocyte-predominant Hodgkin lymphoma—clinical features and treatment outcomes from a 30-year experience. Ann Oncol. 2010 Mar 23, Epub ahead of print.</p> <p>von Wasielewski R, Werner M, Fischer R, Hansmann ML, Hubner K, Hasenclever D, et al. Lymphocyte-predominant Hodgkin's disease. An immunohistochemical analysis of 208 reviewed Hodgkin's disease cases from the German Hodgkin Study Group. Am J Pathol. 1997 Mar;150(3):793-803.</p> <p>Schulz H, rehwald U, Morschhauser F, Elter T, Driessen C, Rudiger T, Borchmann P, Schnell R, Diehl V, Engert A, Reiser M. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSg). Blood 2008; 111: 109-111.</p> <p>Horning SJ, Bartlett NL, Breslin S, Advani RH, Hoppe RT, Ekstrand BC, Lucas JB. Results of a Prospective Phase II Trial of Limited and Extended Rituximab Treatment in Nodular Lymphocyte Predominant Hodgkin's Disease (NLPHD). Blood (ASH Annual Meeting Abstracts) 2007; 110: Abstract # 644.</p> <p>Ekstrand BC, Lucas JB, Horwitz SM, Fan Z, Breslin S, Hoppe RT, et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood. 2003 Jun 1;101(11):4285-9.</p> <p>Nogova L, Reineke T, Brilliant C, Sieniawski M, Rudiger T, Josting A, Bredenfeld H, Skripnitchenko R, Muller RP, Muller-Hermelink K, Diehl V, Engert A. Lymphocyte-predominant and classic hodgkin's lymphoma: a comprehensive analysis from teh German Hodgkin Study Group. J Clin Oncol 2008; 26: 434-439.</p> <p>Rehwald U, Schulz H, Reiser M, Sieber M, Staak JO, Morschhauser F, et al. Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: results of a phase 2 trial of the German Hodgkin Lymphoma Study Group.</p>

<b>Principio attivo</b>	<b><i>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</i></b>
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<b>Principio attivo</b>	<b>Estensione di indicazione relative ad usi consolidati sulla base di evidenze scientifiche presenti in letteratura</b>
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