

FARMACI CON USO CONSOLIDATO NELLE CURE PALLIATIVE (FASE DI TERMINALITA') NELL'ADULTO PER INDICAZIONI ANCHE DIFFERENTI DA QUELLE PREVISTE DAL PROVVEDIMENTO DI AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO
FARE RIFERIMENTO AL DOCUMENTO "FARMACI OFF-LABEL IN CURE PALLIATIVE (CP) PER LA POPOLAZIONE ADULTA" www.aifa.gov.it

Nome principio attivo	Indicazione terapeutica off-label	Referenze di letteratura
<p>Aloperidolo</p>	<p>Somministrazione sottocutanea per agitazione psicomotoria/delirio in fase avanzata di malattia (pazienti con aspettativa di vita presumibile < 3 mesi).</p>	<p><u>Jackson K. et al</u>, <i>Drug therapy for delirium in terminally ill patients</i>. Cochrane Database of Syst Rev 2004</p> <p><u>Candy B. et al</u>, <i>Drug therapy for delirium in terminally ill adult patients</i>. Cochrane Database Syst Rev. 2012</p> <p><u>Caraceni A. et al</u>, <i>Palliating delirium in patients with cancer</i>. Lancet Oncol. 2009</p> <p><u>Centeno C. et al</u>, <i>Delirium in advanced cancer patients</i>. Pall. Med. 2004</p> <p><u>Hui D. et al</u>, <i>Neuroleptics in the management of delirium in patients with advanced cancer</i>. Current Opinion 2016</p> <p><u>Lonergan E. et al</u>, <i>Antipsychotics for delirium</i>. Cochrane Database of Syst Rev 2007</p>
	<p>Somministrazione sottocutanea per il controllo di nausea/vomito/singhiozzo in pazienti che necessitano di terapia sintomatica di supporto in fase avanzata di malattia (aspettativa di vita presumibile < 3 mesi).</p>	<p><u>Murray-Brown F. et al</u>, <i>Haloperidol for the treatment of nausea and vomiting in palliative care patients (Review)</i>. Cochrane Library 2015</p> <p><u>Vella-Brincat J. et al</u>, <i>Haloperidol in palliative care</i>. Palliative medicine 2004</p>

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		<p><u>Critchley P. et al</u>, <i>Efficacy of haloperidol in the treatment of nausea and vomiting in the palliative patient: a systemic review</i>. J Pain Symptom Manage 2001</p> <p><u>Hardy J.R. et al</u>, <i>The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer</i>. J Pain Symptom Manage 2010</p> <p><u>Perkins P. et al</u>, <i>Haloperidol for the treatment of nausea and vomiting in palliative care patients</i>. Cochrane Database Syst Rev. 2009</p> <p><u>Gordon P. et al</u>, <i>Nausea and vomiting in advanced cancer</i>. European Journal of Pharmacology 2014</p> <p><u>Gupta M. et al</u>, <i>Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol</i>. J Support Oncol 2013</p> <p><u>McLean S.L. et al</u>, <i>Using haloperidol as an antiemetic in palliative care: informing practice through evidence from cancer treatment and postoperative contexts</i>. J Pain Palliat Care Pharmacother. 2013</p> <p><u>Walsh D. et al</u>, <i>2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer</i>. Support Care Cancer. 2017</p>
Butilscolamina-	Somministrazione sottocutanea, anche in combinazione con altri farmaci, in infusione continua.	<u>Barcia E. et al</u> , <i>Compatibility of haloperidol and hyoscine-N-butyl bromide in mixtures for subcutaneous infusion to cancer patients in</i>

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ioscina butilbromuro		<p><i>palliative care</i>. Support Care Cancer 2003</p> <p><u>Barcia E. et al</u>, <i>Stability and compatibility f binary mixtures of morphine hydrochloride with hyoscine N- butyl bromide</i>. Support Care Cancer 2005</p> <p><u>Negro S. et al</u>, <i>Morphine, haloperidol and hyoscine N-butyl bromide combined in sc infusion solutions: compatibility and stability evaluation in terminal oncology patients</i>. Int J Pharm 2006</p> <p><u>Barcia E. et al</u>, <i>Tramadol and hyoscine N-butyl bromide combined in infusion solutions: compatibility and stability</i>. Support Care Cancer 2007</p> <p><u>Negro S. et al</u>, <i>Compatibility and stability of ternary admixtures of tramadol, haloperidol, and hyoscine</i>. J Palliat Med 2010</p>
	<p>Somministrazione sottocutanea/endovenosa per ridurre le secrezioni tracheobronchiali nel paziente in cure palliative in fase terminale di malattia (aspettativa di vita presumibile < 2 settimane).</p>	<p><u>Clark K. et al</u>, <i>A pilot phase II randomized, cross-over, double-blinded, controlled efficacy study of octreotide versus hyoscine hydrobromide for control of noisy breathing at the end-of-life</i>. J Pain Palliat Care Pharmacother. 2008</p> <p><u>Likar R. et al</u>, <i>A Clinical Study Examining the Efficacy of Scopolamin-Hydrobromide in Patients with Death Rattle (A Randomized, Double-Blind, Placebo-Controlled Study)</i>. Z Palliative med 2002</p> <p><u>Likar R. et al</u>, <i>Efficacy of glycopyrronium bromide and scopolamine hydrobromide in patients with death rattle: a randomized controlled</i></p>

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		<p><i>study. Eur J Med 2008</i></p> <p><u>Wildiers H. et al</u>, <i>Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. J Pain Symptom Manage 2009</i></p> <p><u>Mercadante S. et al</u>, <i>Refractory death rattle: deep aspiration facilitates the effects of antisecretory agents. J Pain Symptom Manage 2011</i></p>
	<p>Somministrazione sottocutanea/endovenosa per ridurre le secrezioni gastrointestinali nell'ostruzione gastrointestinale non responsiva a trattamenti guaritivi chirurgici o farmacologici nel paziente in cure palliative con breve aspettativa di vita (presumibile < 3 mesi).</p>	<p><u>Ripamonti C. et al</u>, <i>Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. J Pain Symptom Manage 2000</i></p> <p><u>Ripamonti C.I. et al</u>, <i>Management of malignant bowel obstruction. Eur J Cancer 2008</i></p> <p><u>Klein C. et al</u>, <i>Pharmacological treatment of malignant bowel obstruction in severely ill and dying patients: a systematic literature review. Schmerz. 2012.</i></p>
<p>Desametasone</p>	<p>Somministrazione orale/endovenosa/sottocutanea per nausea e vomito in pazienti in fase avanzata di malattia.</p>	<p><u>Gupta M. et al</u>, <i>Nausea and Vomiting in Advanced Cancer- "The Cleveland Clinic Protocol". Journal Supportive Oncology 2013</i></p> <p><u>Vayne-Bossert P. et al</u>, <i>Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to</i></p>

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		<p>chemotherapy, radiotherapy, or surgery). Cochrane Database Syst Rev. 2017</p> <p><u>Davis M.P. et al</u>, <i>Palliative Medicine Study Group of the Multinational Association of Supportive Care in Cancer. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation.</i> J Pain Symptom Manage. 2010</p>
	Somministrazione endovenosa/sottocutanea per occlusione intestinale nei pazienti in fase terminale di malattia.	<p><u>Berger J. et al</u>, <i>Medical Therapy of Malignant Bowel Obstruction with Octreotide, Dexamethasone and Metoclopramide.</i> Am J Hosp Palliat Care. 2016</p> <p><u>Feuer D.J. et al</u>, <i>Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer.</i> Cochrane Database Syst Rev. 2000</p>
	Somministrazione endovenosa/sottocutanea per dispnea nei pazienti in fase terminale di malattia.	<p><u>Hui D. et al</u>, <i>Dexamethasone for Dyspnea in Cancer Patients: A Pilot Double-Blind, Randomized, Controlled Trial.</i> Pain Symptom Manage. 2016</p>
	Somministrazione endovenosa/sottocutanea per compressione midollare in pazienti oncologici in fase terminale.	<p><u>Skeoch G.D. et al</u>, <i>Corticosteroid Treatment for Metastatic Spinal Cord Compression: A Review.</i> Global Spine J. 2017</p> <p><u>Kumar A. et al</u>, <i>Metastatic Spinal Cord Compression and Steroid Treatment: A Systematic Review.</i> Clin Spine Surg. 2017</p> <p><u>Sodji Q. et al</u>, <i>Management of Metastatic Spinal Cord Compression.</i> South Med J. 2017</p>
	Somministrazione orale/endovenosa/sottocutanea	<p><u>Leppert W. et al</u>, <i>The role of corticosteroids in the treatment of pain</i></p>

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	<p>come adiuvante della terapia antalgica in pazienti in fase avanzata di malattia.</p>	<p><i>in cancer patients</i>. Curr Pain Headache Rep. 2012</p> <p><u>Mercadante S. et al</u>, <i>A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients</i>. Am J Hosp Palliat Care. 2007</p> <p><u>Mishra S. et al</u>, <i>Management of neuropathic cancer pain following WHO analgesic ladder: a prospective study</i>. Am J Hosp Palliat Care. 2008</p>
	<p>Somministrazione orale/endovenosa/sottocutanea per astenia e sindrome anoressia-cachessia nei pazienti in fase avanzata di malattia.</p>	<p><u>Yennurajalingam S. et al</u>, <i>Effects of Dexamethasone and Placebo on Symptom Clusters in Advanced Cancer Patients: A Preliminary Report</i>. Oncologist. 2016</p> <p><u>Mücke M. et al</u>, <i>Pharmacological treatments for fatigue associated with palliative care</i>. Cochrane Database Syst Rev. 2015</p> <p><u>Hatano Y. et al</u>, <i>Pharmacovigilance in hospice/palliative care: the net immediate and short-term effects of dexamethasone for anorexia</i>. BMJ Support Palliat Care. 2016</p> <p><u>Tanguy-Goarin C. et al</u>, <i>Drugs administration by subcutaneous injection within palliative care</i>. Therapie. 2010</p> <p><u>Walker J. et al</u>, <i>Evidence-based practice guidelines: a survey of subcutaneous dexamethasone administration</i>. Int J Palliat Nurs. 2010</p>

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Gabapentin	Trattamento del dolore neuropatico.	<p><u>Caraceni A. et al</u>, <i>Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial From the Gabapentin Cancer Pain Study Group</i>. J Clin Oncol 2004</p> <p><u>Matthew T. et al</u>, <i>Treatment of neuropathic pain</i>. Curr Tret Options Neurol 2015</p> <p><u>Deng Y. et al</u>, <i>Clinical practice guidelines for the management of neuropathic pain: a systematic review</i>. BMC Anesthesiol 2016</p> <p><u>Keskinbora K. et al</u>, <i>Gabapentin and an Opioid Combination Versus Opioid Alone for the Management of Neuropathic Cancer Pain: A Randomized Open Trial</i>. J Pain Symptom Manage 2007</p>
Metoclopramide	Somministrazione endovenosa/sottocutanea per nausea e vomito, occlusione intestinale incompleta, anoressia da gastroparesi nei pazienti in cure palliative con breve aspettativa di vita (presumibile < 3 mesi) anche per periodi superiori a 5 giorni, se il beneficio atteso supera il rischio.	<p><u>Davis M.P. et al</u>, <i>Palliative Medicine Study Group of the Multinational Association of Supportive Care in Cancer. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation</i>. J Pain Symptom Manage. 2010</p> <p><u>Bruera E. et al</u>, <i>A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer</i>. J Pain Symptom Manage 2000</p> <p><u>Walsh D. et al</u>, <i>2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer</i>. Support Care Cancer. 2017</p>

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		<p><u>van der Meer Y.G. et al</u>, <i>Should we stop prescribing metoclopramide as a prokinetic drug in critically ill patients?</i> Critical Care 2014</p> <p><u>Gupta M. et al</u>, <i>Nausea and Vomiting in Advanced Cancer- “The Cleveland Clinic Protocol”</i>. Journal Supportive Oncology, 2013</p> <p><u>Collis E. et al</u>, <i>Nausea and vomiting in palliative care</i>. BMJ 2015</p> <p><u>Berger J. et al</u>, <i>Medical Therapy of Malignant Bowel Obstruction With Octreotide, Dexamethasone, and Metoclopramide</i>. Am J Hosp Palliat Care. 2016</p> <p><u>Bruera E. et al</u>, <i>Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen</i>. J Pain Symptom Manage 1996</p> <p><u>Glare P. A. et al</u>, <i>Treatment of Nausea and Vomiting in Terminally Ill Cancer Patients</i>. Drugs. 2008</p>
	<p>Somministrazione endovenosa/sottocutanea per singhiozzo nei pazienti in cure palliative con breve aspettativa di vita (presumibile < 3 mesi) anche per periodi superiori a 5 giorni, se il beneficio atteso supera il rischio.</p>	<p><u>Madanagopalan N.</u>, <i>Metoclopramide in hiccup</i>. Curr Med Res Opin. 1975</p> <p><u>Moretto E.N. et al</u>, <i>Interventions for treating persistent and intractable hiccups in adults (review)</i>. The Cochrane Library 2013</p> <p><u>Wang T. et al</u>, <i>Metoclopramide for patients with intractable hiccups: a multicentre, randomised, controlled pilot study</i>. Intern Med J. 2014</p>

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		<p><u>Jeon Y.S. et al</u>, <i>Management of hiccups in palliative care patients</i>. BMJ Support Palliat Care. 2017</p>
<p>Midazolam</p>	<p>Somministrazione endovenosa/intramuscolare/ sottocutanea/orale per agitazione psicomotoria/delirium per pazienti in fase terminale.</p>	<p><u>Franken L.G. et al</u>, <i>Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients</i>. Br J Clin Pharmacol. 2017</p> <p><u>Franken L.G. et al</u>, <i>Pharmacokinetic considerations and recommendations in palliative care, with focus on morphine, midazolam and haloperidol</i>. Expert Opin Drug Metab Toxicol. 2016</p> <p><u>Bobb B.</u>, <i>A Review of Palliative Sedation</i>. Nurs Clin North Am. 2016</p> <p><u>Lindqvist O. et al</u>, <i>Four essential drugs needed for quality care of the dying: a Delphi-study based international expert consensus opinion</i>. J Palliat Med. 2013</p> <p><u>Lawlor P.G. et al</u>, <i>Delirium in patients with cancer: assessment, impact, mechanisms and management</i>. Nat Rev Clin Oncol. 2015</p> <p><u>Chakraborti D. et al</u>, <i>Melatonin and melatonin agonist for delirium in the elderly patients</i>. Am J Alzheimers Dis Other Demen. 2015</p> <p><u>Gonçalves F. et al</u>, <i>A Protocol for the Control of Agitation in Palliative Care</i>. American Journal of Hospice & Palliative Medicine® 2016</p> <p><u>Lawlor P.G. et al</u>, <i>Delirium in patients with cancer: assessment,</i></p>

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		<i>impact, mechanisms and management. Nat Rev Clin Oncol. 2015</i>
	Somministrazione endovenosa/intramuscolare/sottocutanea per convulsioni in pazienti in fase terminale.	<p><u>Leon Ruiz M. et al</u>, <i>Guidelines for seizure management in palliative care: Proposal for an updated clinical practice model based on a systematic literature review. Neurologia. 2017</i></p> <p><u>Harris N. et al</u>, <i>Seizure management in children requiring palliative care: a review of current practice. BMJ Support Palliat Care. 2017</i></p>
	Somministrazione sottocutanea/intramuscolare per sedazione periprocedurale (ad esempio durante manovre terapeutiche/assistenziali) in pazienti in fase avanzata di malattia e non in fase di terminalità.	<p><u>Schildmann E.K. et al</u>, <i>Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. Pain Symptom Manage. 2015</i></p> <p><u>De Graeff A. et al</u>, <i>Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. J Palliat Med. 2007</i></p> <p><u>Simon S.T. et al</u>, <i>Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev. 2016</i></p> <p><u>Morita T. et al</u>, <i>Ethical validity of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan. Palliative Medicine, Rehabilitation, and Psycho-Oncology Study Group. J Pain Symptom Manage. 2005</i></p> <p><u>Bartz L. et al</u>, <i>Subcutaneous administration of drugs in palliative care: results of a systematic observational study. J Pain Symptom</i></p>

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	<p>Somministrazione endovenosa/intramuscolare/ sottocutanea per la sedazione palliativa di tutti i sintomi che causano angoscia e sofferenza, che non rispondono al trattamento con farmaci specifici, nel paziente terminale.</p>	<p>Manage. 2014</p> <p><u>Bleasel M.D. et al</u>, <i>Plasma concentrations of midazolam during continuous subcutaneous administration in palliative care</i>. Palliat Med. 1994</p> <p><u>Levy M.H. et al</u>, <i>Sedation for the relief of refractory symptoms in the imminently dying: a fine intentional line</i>. Semin Oncol. 2005</p> <p><u>Pecking M. et al</u>, <i>Absolute bioavailability of midazolam after subcutaneous administration to healthy volunteers</i>. Br J Clin Pharmacol. 2002</p> <p><u>Mercadante S. et al</u>, <i>Attitudes of palliative home care physicians towards palliative sedation at home in Italy</i>. Support Care Cancer. 2017</p> <p><u>Calvo-Espinos C. et al</u>, <i>Palliative sedation for cancer patients included in a home care program: a retrospective study</i>. Palliat Support Care. 2015</p> <p><u>Daniel S. et al</u>, <i>Improving the accuracy and turn-around time of controlled drug prescribing for patients being discharged home for end-of-life care</i>. BMJ Qual Improv Rep. 2014</p> <p><u>Mercadante S. al</u>, <i>Palliative sedation in patients with advanced cancer followed at home: a prospective study</i>. J Pain Symptom Manage. 2014</p>

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		<p><u>Alonso-Babarro A. et al</u>, <i>At-home palliative sedation for end-of-life cancer patients</i>. Palliat Med 2010</p>
<p>Morfina solfato/Morfina cloridrato</p>	<p>Somministrazione per trattamento della dispnea incontrollata che non risponde alla terapia della patologia di base nel paziente in fase avanzata di malattia.</p>	<p><u>Ben-Aharon I.</u>, <i>Interventions for alleviating cancer-related dyspnea: A systematic review and meta-analysis</i>. Acta Oncol 2012.</p> <p><u>Clemens K.E. et al</u>, <i>Symptomatic Therapy of Dyspnea with Strong Opioids and Its Effect on Ventilation in Palliative Care Patients</i>. J Pain Symptom Manage 2007</p> <p><u>Gomutbutra P. et al</u>, <i>Management of Moderate-to-Severe Dyspnea in Hospitalized Patients Receiving Palliative Care</i>. J Pain Symptom Manage 2013</p> <p><u>Jennings A.L. et al</u>, <i>Opioids for the palliation of breathlessness in advanced disease and terminal illness</i>. Cochrane Database Syst Rev 2012</p> <p><u>Burke A.L.</u>, <i>Palliative care: an update on "terminal restlessness"</i>. Med J Aust. 1997</p> <p><u>Strieder M. et al</u>, <i>Symptomatic treatment of dyspnea in advanced cancer patients : A narrative review of the current literature</i>. Wien Med Wochenschr. 2017</p> <p><u>Kloke M. & Cherny N., on behalf of the ESMO Guidelines Committee</u>: <i>Treatment of dyspnoea in advanced cancer patients</i>:</p>

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		ESMO Clinical Practice Guidelines. Annals of Oncology 2015.
Octreotide	Trattamento del vomito nel paziente in fase avanzata di malattia.	<p><u>Gordon P. et al</u>, <i>Nausea and vomiting in advanced cancer</i>. Eur J Pharmacol 2014</p> <p><u>Gupta M. et al</u>, <i>Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol</i>. J Support Oncol 2013</p> <p><u>Ang S.K. et al</u>, <i>Nausea and vomiting in advanced cancer</i>. Am J Hosp Palliat Care 2010</p>
	Trattamento dell'occlusione intestinale sintomatica nel paziente in fase avanzata di malattia.	<p><u>Mercadante S. et al</u>, <i>Medical Treatment for Inoperable Malignant Bowel Obstruction: A Qualitative Systematic Review</i>. J Pain Symptom Manage 2007</p> <p><u>Mercadante S. et al</u>, <i>Octreotide for malignant bowel obstruction: Twenty years after</i>. Crit Rev Oncol Hematol 2012</p> <p><u>Ripamonti C.I. et al</u>, <i>Management of malignant bowel obstruction</i>. Eur J Cancer 2008</p> <p><u>Gordon P. et al</u>, <i>Nausea and vomiting in advanced cancer</i>. Eur J Pharmacol 2014</p> <p><u>Gupta M. et al</u>, <i>Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol</i>. J Support Oncol 2013</p>

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		<p>Watari H. et al, <i>A prospective study on the efficacy of octreotide in the management of malignant bowel obstruction in gynecologic cancer</i>. Int J Gynecol Cancer. 2012</p> <p><u>Berger J. et al</u>, <i>Medical Therapy of Malignant Bowel Obstruction With Octreotide, Dexamethasone, and Metoclopramide</i>. Am J Hosp Palliat Care. 2016</p> <p><u>Faisinger R.L. et al</u>, <i>Symptom control in terminally ill patients with malignant bowel obstruction (MBO)</i>. J pain Symptom Manage 1994</p> <p><u>Krouse R.S.</u>, <i>The international conference on malignant bowel obstruction: a meeting of the minds to advance palliative care research</i>. J Pain Symptom Manage 2007</p>