




		EMLc	ATC codes: A02BC01
Indication	Gastrointestinal bleeding	ICD11 code: ME24.9Z	
INN	Omeprazole		
Medicine type	Chemical agent		
List type	Core		
Formulations	Parenteral > General injections > IV: 40 mg in vial (EML) Oral > Liquid: 20 mg powder for oral liquid ; 40 mg powder for oral liquid Oral > Solid: 10 mg ; 20 mg ; 40 mg		
EML status history	First added in 2009 (TRS 958) Changed in 2015 (TRS 994)		
Sex	All		
Age	Also recommended for children		
Therapeutic equivalence	Medicines within the same pharmacological class can be used		
Patent information	Patents have expired in most jurisdictions Read more about patents . 		
Wikipedia	Omeprazole 		
DrugBank	Omeprazole 		

Summary of evidence and Expert Committee recommendations

Omeprazole (as solid and liquid oral dose forms) is currently included on the EML and EMLc with a square box as representative of the therapeutic class of proton-pump inhibitors (PPIs). The need for a parenteral preparation of omeprazole was discussed at the 19th meeting of the Expert Committee in 2013 as part of a broader review of antiulcer medicines (histamine-2 receptor antagonists (H2RAs) and PPIs). In 2013, the Expert Committee considered that the most important and common indication for intravenous PPIs was peptic ulcer bleeding. However, no changes to the EML were recommended at that time and it was considered that a more extensive application would be needed to justify the addition of a parenteral PPI on the EML (1). An application was submitted by Dr Grigorios Leontiadis and Dr Holger Schünemann, Departments of Clinical Epidemiology and Biostatistics & WHO Collaborating Centre for Evidence-Informed Policy, McMaster University, Hamilton, ON, Canada, for inclusion on the core list of the EML of a parenteral formulation of omeprazole for intravenous administration for: • patients with severe suspected non-variceal upper gastrointestinal bleeding for whom endoscopy is unavailable or is expected to be delayed; and • patients with endoscopically documented peptic ulcer bleeding with high risk for detrimental outcomes (active bleeding or a non-bleeding visible vessel), regardless of the application of endoscopic haemostatic treatment (which may not be widely available in low-resource settings). Expert reviews of the application were prepared by two members of the Expert Committee. Comments in support of the application were received from Myriam Henkens, International Medical Coordinator, Médecins Sans Frontières. In consideration of the application, the Expert Committee acknowledged that peptic ulcer bleeding is a common medical emergency and is associated with substantial morbidity, mortality and health-care costs (2). Haemostasis in the stomach and duodenum is antagonized by gastric acid and pepsin, which inhibit clot formation and promote lysis of previously formed clots. The Committee noted that, in a Cochrane systematic review of 24 randomized controlled trials comprising 4373 participants, PPIs improved clinical outcomes in patients with peptic ulcer bleeding compared with H2RAs or placebo (3). PPI treatment significantly reduced rebleeding (odds ratio (OR) 0.49; 95% CI: 0.37–0.65), surgical interventions (OR 0.61; 95% CI 0.48–0.78) and further endoscopic haemostatic treatment

(OR 0.32; 95% CI: 0.20–0.51). There was no evidence of an effect of PPI treatment on all-cause mortality rates (OR 1.01; 95% CI 0.74–1.40). However, PPI treatment significantly reduced mortality when the analysis was restricted to patients with high-risk endoscopic findings (active bleeding or a non-bleeding visible vessel) (OR 0.53; 95% CI: 0.31–0.91), and among trials that had been conducted in Asia (OR 0.35; 95% CI: 0.16–0.74). In the current application, a literature search for clinical practice guidelines on the management of peptic ulcer bleeding or non-variceal upper gastrointestinal bleeding was performed. Of the seven guidelines identified (4–10), six recommended pre-endoscopic PPI treatment in patients with suspected non-variceal upper gastrointestinal bleeding and none recommended an exclusively oral route of administration. All seven guidelines recommended post-endoscopic PPI treatment of patients with endoscopically documented peptic ulcer bleeding. Again, none recommended an exclusively oral route of administration. The application also presented an updated systematic review of 10 randomized controlled trials that compared oral with intravenous PPI treatment in patients with peptic ulcer bleeding (11). The pooled analysis showed no statistically significant differences in mortality rates, rebleeding rates or surgery rates between IV and oral PPI treatment, therefore suggesting equivalence. The summary of findings is presented in Table 10, pages 327–328 of the Technical Report (TRS 994). The Expert Committee acknowledged the fact that biases related to study limitations (i.e. absence of blinding) postulated by Cochrane reviewers, which led to downgrading of the quality of evidence to low or very low, were unlikely to happen. Blinding of outcome assessors is less important for the assessment of all-cause mortality. It is possible that bleeding and surgery might be more vulnerable to biased judgments in unblinded RCTs. However the Expert Committee perceived these risks to be limited, while indirectness and imprecision might be more important limitations to overall quality of evidence. With regard to safety, short-term treatment with PPIs (oral or IV) for the duration of therapy required for peptic ulcer bleeding (median 2–3 days) has not raised safety concerns (12). The 2006 Cochrane review that compared PPIs with placebo or H2RAs for peptic ulcer bleeding found that there were no serious adverse effects associated with PPI treatment (oral or IV) (3). The 10 trials included in the application's systematic review of IV versus oral PPI provided limited data on adverse effects. While the data presented in the application were not specific to omeprazole, the Expert Committee was satisfied that the efficacy and safety of intravenous PPIs for peptic ulcer bleeding was acceptable. The Committee noted that other available parenteral PPIs include esomeprazole, lansoprazole and pantoprazole, and that there was no evidence to suggest significant differences in the efficacy and safety of omeprazole compared with other PPIs. This view was supported by the fact that oral dose forms of omeprazole were included in the Model Lists in 2009 with a square box symbol indicating similar clinical performance to other agents within the same pharmacological class. No specific data on the cost of IV omeprazole were presented. The median supplier price for omeprazole 20 mg oral tablets/capsules is reported by the International Drug Price Indicator Guide as US\$ 0.0213 per tablet/capsule. The Committee noted that the daily cost of IV pantoprazole (then on patent) was US\$ 7.64 in the USA in 2003; since pantoprazole came off patent in 2007, it was likely that the cost would now have fallen significantly. The Committee considered that it was reasonable to estimate the cost of IV omeprazole to be similar to the cost of IV pantoprazole. The Committee considered that, in settings where endoscopy was not easily and/or immediately available, treatment of suspected or documented peptic ulcer bleeding with IV PPIs represented a potentially life-saving intervention. However, the Committee agreed that PPI treatment and endoscopic haemostatic therapy are not substitutes for each other, and that both treatments are effective in reducing adverse clinical outcomes. On the basis of the evidence presented, the Committee recommended inclusion of the parenteral formulation of omeprazole for IV administration on the core list of the EML for the treatment of adults with suspected peptic ulcer bleeding for whom endoscopy is unavailable or is expected to be delayed, and of patients with confirmed peptic ulcer bleeding with high risk for detrimental outcomes, regardless of the application of endoscopic haemostatic techniques. The Committee considered that it was appropriate for parenteral omeprazole to be listed with the square box symbol, indicative of similar within-class performance of PPIs and for consistency with the listed omeprazole oral dose forms. The Committee also recommended that an application for inclusion of IV omeprazole on the Model List of Essential Medicines for Children should be sought, so that the suitability of the parenteral formulation for the treatment of children could be evaluated. References: 1. 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