Dolcanatide

National Cancer Institute

Source

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An orally administered analog of the human endogenous natriuretic hormone uroguanylin and guanylate cyclase C (GC-C) agonist, with potential laxative, anti-nociceptive and anti-inflammatory activities. Upon administration, dolcanatide, by mimicking uroguanylin, binds to and activates GC-C locally on endothelial cells in the gastrointestinal (GI) tract, without entering the systemic circulation. Activation of GC-C results in an increase in cyclic guanosine monophosphate (cGMP). Increased concentrations of cGMP lead to the activation of the anion channel cystic fibrosis transmembrane conductance regulator (CFTR). CFTR activation increases the secretion of negatively charged ions, particularly chloride and bicarbonate, into the GI tract lumen, which further drives sodium ions and then water into the lumen. This leads to increased fluid secretion in the GI tract, accelerated transit and changes in stool consistency. In addition, ion channel modulation may decrease muscle contractions and the activity of pain-sensing nerves, thereby decreasing intestinal pain. Also, GC-C may inhibit the secretion of pro-inflammatory cytokines, which may ameliorate GI inflammation. Uroguanylin, a naturally occurring human GI peptide, is a ligand for GC-C and plays a key role in anti-inflammatory processes in the GI tract.