Memantine received marketing authorization from the European Agency for the Evaluation of Medicinal Products (EMEA) for the treatment of moderately severe to severe Alzheimer’s disease (AD) in Europe on 17th May 2002 and shortly thereafter was also approved by the FDA for use in the same indication in the USA. Memantine is a moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with strong voltage-dependency and fast kinetics. Due to this mechanism of action (MOA), there is a wealth of other possible therapeutic indications for memantine and numerous preclinical data in animal models support this assumption. This review is intended to provide an update on preclinical studies on the pharmacodynamics of memantine, with an additional focus on animal models of diseases aside from the approved indication. For most studies prior to 1999, the reader is referred to a previous review [196]. In general, since 1999, considerable additional preclinical evidence has accumulated supporting the use of memantine in AD (both symptomatic and neuroprotective). In addition, there has been further confirmation of the MOA of memantine as an uncompetitive NMDA receptor antagonist and essentially no data contradicting our understanding of the benign side effect profile of memantine.