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ADVANCES OF EDARAVONE AS A NEUROPROTECTOR

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Edaravone (Eda) is a low-molecular-weight (174.2 g/mol) free radical scavenger of the 2-pyrazolin-5-one class. First approved in Japan for acute ischemic stroke (AIS) in 2001, it received FDA approval for amyotrophic lateral sclerosis (ALS). in 2017, with an oral formulation (Radicava ORS) approved in 2022.

Edaravone primarily removes harmful free radicals (ROS/RNS) that damage brain cells. It stops lipid peroxidation, which prevents membrane damage, and also prevents ferroptosis, a specific type of cell death (Dixon et al., 2012). Beyond direct scavenging, edaravone activates key protective pathways, including Nrf2 for antioxidant defense, BDNF for neuron survival, and PI3K/Akt for general cell survival (Brazil & Hemmings, 2001). At the same time, it blocks harmful pathways such as NF-κB and NLRP3 to reduce inflammation, MAPK/JNK to limit stress-induced cell death, and ER stress to prevent cellular damage responses (Walter & Ron, 2011). These actions affect multiple cell types in the central nervous system, including neurons, microglia, astrocytes, oligodendrocytes, and the cells that form the blood-brain barrier (Abbott et al., 2010).

Oral bioavailability is ~57% due to first-pass metabolism. Edaravone is 92% protein-bound and penetrates the blood-brain barrier (up to 60% reaches brain). Metabolism occurs via phase II conjugation (UGT1A9 predominant; also UGT1A6, 2B7, 2B17 and sulfotransferases), producing inactive sulfate and glucuronide conjugates. Half-life is 4.5–6 hours; excretion is primarily urinary (60–80% as glucuronide). Renal transporters include OAT1/3 (uptake) and BCRP/MRP4 (efflux) (Mizuno et al., 2013).

For ALS, the standard regimen is IV 60 mg over 60 minutes (14 days on, 14 days off) or oral 105 mg daily on an empty stomach. Efficacy is modest, slowing functional decline in early-stage patients (FVC ≥80%, disease duration ≤2 years), Japan, 2017. For AIS (Japan), IV 30 mg twice daily for 14 days reduces infarct volume and improves outcomes. Investigational applications include traumatic brain injury, Alzheimer's, and Parkinson's disease (Ikeda et al., 2018).

Common adverse effects (≥2%) include contusion, gait disturbance, and headache. Serious events (hypersensitivity, nephrotoxicity) are rare. Edaravone contains sodium bisulfite and is contraindicated in patients with sulfite allergies. No clinically significant cardiac effects are observed (Japan, 2017).

Combination therapies improve efficacy: EdaB (with borneol) enhances functional outcomes; t-PA reduces infarct size and mortality; hypothermia synergizes via Nrf2/HO-1; urinary kallidinogenase, oxiracetam, caffeine, and traditional medicines (Shuxuening, Shenxiong) show added benefit. BBB delivery is enhanced by borneol, cucurbiturils, thermosensitive gels, microgels, MR-guided focused ultrasound, and A2AR-targeted micelles.

Annual cost exceeds $167,000. For ALS, ICER exceeds $1.9–$11 million per QALY (not cost-effective). For stroke, edaravone is cost-saving or cost-effective. Insurance policies often impose criteria beyond the FDA label, limiting access.

Edaravone is a pleiotropic neuroprotective agent w.ith established roles in ALS and stroke. Its future depends on optimizing patient selection, validating combination regimens, advancing BBB delivery technologies, and implementing pricing reforms to improve cost-effectiveness and equitable access.