



## Monograph

# Idebenone

## Introduction

Idebenone [2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone] is a synthetic analogue of coenzyme Q10 (CoQ10), the vital cell membrane antioxidant and essential constituent of the ATP-producing mitochondrial electron transport chain (ETC). Idebenone is a potent antioxidant, with the ability to operate under low oxygen tension situations. Because of its ability to inhibit lipid peroxidation, idebenone protects cell membranes and mitochondria from oxidative damage. Its antioxidant properties protect against cerebral ischemia and nerve damage in the central nervous system. Idebenone also interacts with the ETC, preserving ATP formation in ischemic states. This compound has also been shown to stimulate nerve growth factor, a characteristic that could be important in the treatment of Alzheimer's and other neurodegenerative diseases.

## Biochemistry and Pharmacokinetics

Idebenone is rapidly absorbed and reaches peak concentrations in the brain comparable to those in plasma.<sup>1</sup> Animal studies showed a peak plasma level 15 minutes after oral administration, with a half-life of 2.2-15.4 hours. Idebenone was well distributed in tissues, with higher concentrations in the gut, liver, and kidney. Excretion was via both urine and feces, mostly as metabolites.<sup>2</sup> A human pharmacokinetic and safety study found a half-life of 18 hours, with biphasic elimination.<sup>3</sup> Researchers found no long-term tissue accumulation in humans or rats.<sup>2,3</sup>

## Mechanisms of Action

As with other antioxidants, idebenone exists in a reduced and an oxidized state. In a study of idebenone's effect on astroglial cells, idebenone, in either redox state, significantly inhibited the enzymatic metabolism of arachidonic acid by cyclooxygenase and lipoxygenase. This effect was stronger with the reduced form, and showed potential central nervous system anti-inflammatory activity.<sup>4</sup>

Introduction of iron and ascorbate to a cell mixture or a group of isolated cells can establish experimental cellular oxidant injury. Synaptosomes isolated from rat brain cortex were treated with iron and ascorbate. Idebenone prevented both the formation of reactive oxygen species in the cytosol and mitochondria, as well as a decrease in protein-sulfhydryl content (an indicator of protein oxidation), compared to controls.<sup>5</sup>

It appears that, in addition to functioning as an antioxidant, idebenone functions as an electron carrier in the ETC, similar to CoQ10. To illustrate, researchers in Japan introduced idebenone into a canine CoQ10-depleted brain mitochondrial preparation, which prevented the loss of ETC activity normally seen with CoQ10 depletion. Idebenone also inhibited mitochondrial lipid peroxidation,<sup>6</sup> which

can be interpreted as protecting against mitochondrial membrane damage. Other animal studies confirm the mitochondrial membrane protective effects of idebenone.<sup>7,8</sup>

Idebenone treatment of rats with experimental cerebral ischemia inhibited the loss of acetylcholine in forebrain regions, prevented increases in lactate and free fatty acids, and preserved ATP content in the cerebral cortex. These results indicate idebenone protects against ischemic damage and promotes ATP production in the brain.<sup>9,10</sup>

## **Clinical Indications**

### ***Alzheimer's Disease***

Nerve growth factor plays an important role in the growth, survival, and preservation of cholinergic neurons in the central nervous system. In Alzheimer's disease, cholinergic neurons can become damaged and die. In a rat study, oral administration of idebenone stimulated increases in nerve growth factor protein, mRNA, and choline acetyltransferase activity in basal forebrain lesioned rats. Idebenone also improved behavioral deficits in habituation, water maze, and passive avoidance tasks, which suggests idebenone might stimulate nerve growth factor synthesis *in vivo*. Similar results were found in aged rats.<sup>11-13</sup>

Amyloid beta-peptide (ABP), the major constituent of senile plaques in Alzheimer's disease, is neurotoxic, possibly via an oxidative stress mechanism. Rats given an intracerebroventricular infusion of ABP demonstrated significant impairment of memory and behavior, which was prevented when idebenone and alpha tocopherol were given orally before and during ABP infusion.<sup>14</sup> In a double-blind, placebo-controlled multi-center human study, 450 patients were given either placebo for 12 months, followed by idebenone 90 mg three times per day for another 12 months; 90 mg three times per day for 24 months; or 120 mg three times per day for 24 months. Significant dose-dependent improvements were seen in measurements of clinical status and in neuropsychiatric tests compared to placebo. These improvements continued over the two-year study.<sup>15</sup>

Three hundred patients with mild-to-moderate Alzheimer's disease were randomized to receive either placebo, idebenone 30 mg three times per day, or 90 mg three times per day for six months. Statistically significant improvement was noted in the total score of the Alzheimer's Disease Assessment Scale (ADAS-total), and in one cognitive parameter (ADAS-cog). An analysis of therapy responders revealed significant improvement in three outcome measures (clinical global response, ADAS-Cog, and non-cognitive scores) in the idebenone 90 mg three times per day group, compared to placebo.<sup>16</sup> Other studies have confirmed these findings.<sup>17</sup>

### ***Liver Disease***

Oxidative stress has been implicated in a number of hepatic diseases, including bile acid-induced liver injury in hepatic cholestasis, which was evaluated in an *in vitro* study. Treatment with idebenone protected against bile acid-induced rat hepatocellular injury and lipid peroxidation, and prevented hydroperoxide production in hepatic mitochondria.<sup>18</sup>

### ***Cerebrovascular Disease***

In a small human study of nine patients with cerebrovascular disease, 90 mg idebenone was given daily, and electroencephalograms and clinical symptoms were monitored. The results suggested that idebenone supplementation produced improvements in EEG and clinical symptoms in these patients.<sup>19</sup>

### **Friedreich's Ataxia**

Friedreich's ataxia (FA), an autosomal recessive spinal ataxia, is characterized by unsteady gait, weakness, sensory loss, upper extremity ataxia, mental decline, and progressive cardiomyopathy. The pathophysiology of FA is due to a deficiency of frataxin, a protein involved in regulation of mitochondrial iron content, which causes oxidative damage from mitochondrial iron overload. This leads to a deficiency in mitochondrial enzymes, reduced energy output, and mitochondrial damage. Idebenone dosing (5 mg/kg daily for 8 weeks) in FA patients significantly decreased a marker of oxidative DNA damage.<sup>20</sup> Idebenone prevented iron-induced lipoperoxidation and cardiac muscle injury in three patients given 5 mg/kg daily for 4-9 months, resulting in a reduction of left ventricular enlargement in these patients.<sup>21</sup>

### **Dosage and Safety**

Two hundred Alzheimer's disease patients received either 90 mg or 270 mg idebenone per day for six months. No significant adverse events or changes in vital signs, ECG or clinical laboratory parameters were noted.<sup>16</sup> Barkworth et al gave 10 healthy male volunteers 300 mg per day for 35 days. No changes were seen in blood and urine lab values, and the dose was well tolerated.<sup>3</sup> Safety and tolerability of idebenone were good and similar to placebo during a two-year study utilizing doses up to 360 mg per day.<sup>15</sup> A 900 mg per day dose was given to 17 men for four weeks, with no adverse effects seen on electroretinography, auditory evoked potentials, or visual analogue scales.<sup>22</sup>

Idebenone has been found to inhibit platelet aggregation *in vitro*, by inhibition of phospholipase B2 production,<sup>23</sup> which might contraindicate its use in patients already on anti-clotting therapy or in those with a history of – or at risk for – hemorrhagic stroke.

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