Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Ibudilast

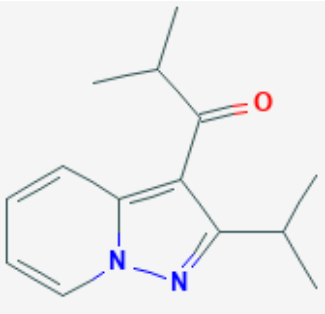
Evidence Summary

Improves circulation, especially to the brain, and may slow neurodegeneration by reducing glial-mediated inflammation. Generally well-tolerated, with less side effects than most non-selective PDE inhibitors.

Neuroprotective Benefit: Can improve blood flow to the brain and may protect against glial-mediated neuroinflammation-induced neurodegeneration.

Aging and related health concerns: May benefit vascular health by improving circulation without affecting blood pressure or heart rate, though only a few small studies have been carried out in humans.

Safety: Low-dose ibudilast has good long-term safety profile. Nausea and gastrointestinal symptoms are primary side effects. Short-term safety profile of high-dose treatment is similar to low-dose, but the long-term effects have not been established.

Availability: Rx in Japan and Korea, Clinical trials in US	**Dose:** 20 mg/day for asthma, 30 mg/day post stroke dizziness 60-100 mg/day tested for CNS disorders. Taken orally in 10 mg capsules	**Chemical formula:** $C_{14}H_{18}N_2O$ **MW:** 230.311 g/mol  Source: PubChem
Half-life: 19 hours	**BBB:** Penetrant	
Clinical trials: Phase 1 RCT for safety, addiction (alcohol, opioids, methamphetamine), and migraine. Phase 2 RCT for addiction, progressive MS (n=255), and ALS (n=108).	**Observational studies:** None	

What is it? Ibudilast (AV-411, MN-166) is a CNS penetrant drug with a broad spectrum of anti-inflammatory activity. It was primarily identified as a non-selective phosphodiesterase (PDE) inhibitor, which preferentially targets PDE 4 and 10, but also has modest affinity for PDE 3 and 11 [1]. Based on the inhibitor constant (K_i), or concentration required for half-maximal inhibition, ibudilast is most potent towards both cAMP and cGMP forms of PDE10A1 (~1-2 mM) and all major isoforms of PDE4 (A, B, C, D) (~3-6 mM), followed by the cAMP forms of PDE11A1 and PD3A (~9 mM) [2]. In terms of PDE4, only one isoenzyme of each isoform was examined (A4, B2, C2, and D3), so it is not known whether ibudilast has further selectivity amongst the isoenzymes, which might influence its therapeutic profile.

PDE inhibitors increase levels of cyclic nucleotides, such as cAMP and cGMP, which play important roles in cell signaling, reduction of pro-inflammatory cytokines, and the production of neurotrophic factors [3]. Ibudilast is also a leukotriene receptor antagonist, has anti-nociceptive effects, and suppresses glial activation [1]. It has been marketed in Japan, under the brand name Ketas®, for 30 years for asthma and post-stroke dizziness based on its bronchodilatory and cerebral vasodilatory effects, respectively. It is also available as an ophthalmic solution for the treatment of eye allergies. At the recommended doses for these indications, it has a good safety record, and is associated with a lower incidence of gastrointestinal side effects than other available non-selective PDE inhibitors [1]. In recent years, MedicNova has been developing Ibudilast (MN-116) at higher doses for the treatment of CNS related diseases, including addiction, amyotrophic lateral sclerosis, and multiple sclerosis [4].

Neuroprotective Benefit: Can improve blood flow to the brain and may protect against glial-mediated neuroinflammation-induced neurodegeneration.

Types of evidence:

- 4 RCT (Phase 1 RCT: Methamphetamine dependence n=11; Relapse-remitting MS n=297, Progressive MS n=255, ALS n=108)
- 3 non-controlled clinical studies (Post-stroke dizziness, n=5, 9, 11)
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

While the ability of ibudilast to regulate cognitive function has not been directly tested, its clinically demonstrated abilities to **increase cerebral blood flow, and slow the rate of brain atrophy** in the context of neurodegeneration suggest that it may protect against processes associated with cognitive decline [1; 5]. In a Phase 1 RCT in people with methamphetamine dependence (n=11), improved performance on the Conners' continuous performance test-II (CPT-11) suggests ibudilast may have a protective effect on sustained attention or executive function during early abstinence [6]. Several studies also indicate that it may also help counteract against deleterious processes associated with depression, as individuals with higher levels of depressive symptoms appeared to have preferential benefit [7; 8; 9] . The neuroprotection is primarily attributed to **a shift away from pathogenic pro-inflammatory signaling by chronically activated glial cells in the brain, and towards protective glial functions, such as the secretion of neurotrophic factors** [10].

Stroke-related vertigo: Benefit

Ibudilast (30 mg/daily) is approved in Japan for the treatment of post-stroke dizziness based on clinical benefit demonstrated in RCTs. Small imaging studies (n=5, 9, 11) have revealed that ibudilast increases cerebral blood flow following both acute and chronic administration [7; 11; 12]. The resolution of vertigo following treatment with ibudilast for 3 months was **associated with increased blood flow to the occipital cortex** [7; 11]. A similar increase in the occipital cortex was seen in response to a drug used for visual vertigo (acetazolamide), suggesting this change in blood flow may drive the clinical efficacy [11]. Depressive patients also showed significant improvement on the Japan Stroke Depression scale [7], though it is unclear whether this effect is also mediated by increased cerebral blood flow, reduction in neuroinflammation, induction of neurotrophic factors, or an alternative mechanism.

Progressive Multiple Sclerosis: Potential Benefit

While relapsing-remitting MS (RRMS) is driven by discrete attacks of myelin by inflammatory lymphocytes, progressive MS is characterized by a steady accumulation of disability that is thought to involve chronic pathogenic microglial activation [13]. Progressive MS patients also experience both gray and white matter neurodegeneration.

Ibudilast (30 mg or 60 mg/day) was unsuccessful in reducing inflammatory relapses in a placebo-controlled Phase 2 trial (n=297) for RRMS, but a **reduction in the percentage of brain volume change** (0.8% vs 1.2%, p=0.04), and possible decrease in depression was seen in the 60 mg group [14]. Ibudilast (100 mg/day) also showed neuroprotective effects in reducing brain atrophy in a placebo-controlled Phase 2 trial (NCT01982942) (n=255) for progressive MS [5]. The brain parenchymal fraction (BPF) is the brain size relative to the volume of the outer surface contour of the brain. There was a **2.5 mL reduction in the loss of brain size over 2 years**, as indicated by a lower rate of change in the BPF [ibudilast -0.0010/year vs. placebo -0.0019/year, difference, 0.0009; 95% Confidence Interval (CI), 0.00004 to 0.0017; P=0.04). Cortical thickness was also protected with ibudilast treatment (-0.0019 (95% CI -0.0061 to 0.0022) vs -0.0105 (95% CI -0.0146 to -0.0065) difference = 0.0086 (95% CI 0.0028 to 0.0144)]. It remains to be determined whether the apparent neuroprotective effects are mediated by a reduction in microglial activation. Similar to other neurodegenerative diseases, there is a poor track record of Phase 2 measures translating to clinically meaningful benefits for progressive MS patients [15], so a larger Phase 3 study is needed to confirm benefit.

Amyotrophic Lateral Sclerosis: Potential Benefit

ALS involves the degeneration of motor neurons, and is clinically characterized by the population of motor neurons that are first affected by the disease [16]. Limb-onset ALS is the most common form with initial symptoms occurring in the arms and legs. Bulbar-onset ALS initially affects muscles involved in speaking, breathing, and swallowing and tends to progress more rapidly.

In a recent Phase 2 RCT (NCT02238626) for ALS (n=41 without ventilation, n=67 with non-invasive ventilation) where ibudilast (60 mg/day) was tested as an add-on therapy to riluzole (100 mg), benefits appeared to be largely restricted to those with the bulbar form. Bulbar ALS patients with (n=39/67) or without (n=31/41) ventilation **on ibudilast were more likely be responders**, as defined by an improvement on the ALS Functional rating scale revised (ALSFRS-R), than those treated with riluzole alone (26.9% vs 7.7% p=0.1644, and 30% vs 9.1% p=0.1916, respectively) (Press release). The only statistically significant benefit was seen with the percentage of responders on the ALS assessment

questionnaire (ALSAQ-5) in bulbar ALS patients without ventilation (60% vs 9.1% p=0.0071). Based on the results from this Phase 2 trial, MedicNova received positive feedback from the FDA in late 2018 regarding its development plan for a larger Phase 3 trial including patients with all forms of ALS (Press release).

It is not clear whether the observed benefits are related to reductions in neuroinflammation and/or preservation of motor neurons. An ongoing Phase 1/2 open-label **biomarker study** (NCT02714036) (n=35) **is expected to address whether high-dose ibudilast (100 mg) alters markers of central and peripheral inflammation.** PET imaging with [11C]-PBR28 will be used to assess CNS inflammation in the motor cortices and brain stem, since peripheral benzodiazepine receptors (PBR) are upregulated on activated microglia. [^{11}C]-PBR28 is a second generation 18-kDa translocator protein (TSPO) ligand (PBR = TSPO). It will be important to see whether clinical efficacy is associated with a decrease in inflammation.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: Potential benefit (preclinical)

Ibudilast has not been well-studied in the context of Alzheimer's disease (AD), but studies examining genetic risk factors for AD suggest that chronic microglial activation may play an important role in driving neurotoxic inflammation [17]. Therefore, drugs which can mitigate glial activation are projected to have therapeutic promise [18]. Ibudilast is an interesting candidate because it does not deplete microglia, but rather, it shifts their responses from pro-inflammatory to neuroprotective [10]. Additionally, PDE3 and PDE4 inhibitors have been shown to exhibit cognitive enhancing effects in preclinical studies and in some small clinical studies [19].

Since the benefit of PDE inhibitors is thought to relate to whether baseline levels are increased or decreased, it will be important to have a better understanding of how different PDE isoforms are altered in the AD brain. There is **not a clear consensus on how PDE levels are affected in AD** based on the studies conducted thus far, and the effects are isoform specific [19]. It is possible that only a subpopulation of patients with high levels of PDE4 and PDE10 would derive significant benefit from ibudilast.

In neuron-glia co-culture, ibudilast has been shown to dose-dependently **suppress oxidative stress and pro-inflammatory mediators** (ROS, IL-1β, TNF-α), while increasing anti-inflammatory IL-10, and

neurotrophins (NGF, GDNF, NT-4) in LPS-activated microglia, and improving neuron survival from 20-68% [10]. Ibudilast was also shown to protect against glutamate-mediated excitotoxicity in hippocampal neurons in a cAMP dependent manner [20], and H_2O_2 induced apoptosis in astrocytes in a cGMP dependent manner [21]. Ibudilast (12 mg/kg/day) pretreatment was neuroprotective in a mouse model of $A\beta_{1-42}$ induced neurotoxicity by preventing the induction of proinflammatory cytokines (NF-kb, TNFα), and pro-apoptotic caspase-3 activation [22]. Ibudilast treatment prevented spatial learning and memory impairments, based on performance on the Morris water maze and Y-maze. Memory performance was not affected by ibudilast in healthy male mice.

Parkinson's disease: Unclear/Potential harm (preclinical)

Ibudilast was hypothesized to be beneficial for Parkinson's disease (PD) because of its effects on PDE10. PDE10A is a nigrostriatal specific form that is highly enriched in dopaminergic medium spiny neurons [23]. In the MPTP model of PD male mice treated with ibudilast (40-50 mg/kg subcutaneously) 2 days prior through 7 days after MPTP exposure had a reduction glial activation, as indicated by reduced expression of GFAP (98.66±4.82 (50 mg) vs. 122.93±2.52, $P<0.05$) and pro-inflammatory mediators (IL-6, TNFα, and IL-β) [24]. They also showed an increase in striatal levels of the neurotrophic factor GDNF (1.73±0.26 (40 mg) vs. 0.94±0.19, $P<0.05$). However, this **did not translate into protection from acute neuronal loss following MPTP-induced toxicity**. The authors of this study speculate that since persistent glial activation and dysregulation are common in progressive neurological disease, benefits may only be clinically significant in the chronic phase. However, there is evidence to suggest that PDE4 inhibition may be ineffective for PD, or potentially exacerbate cognitive symptoms. PD patients were shown to have reductions in striatal-thalamic PDE4 up to 32 percent, which is hypothesized to contribute to declines in spatial working memory [25]. Based on studies with rolipram, it is thought that cAMP-specific PDE4 inhibition may impair cognition in a context where PDEs are already downregulated [26]. Since ibudilast is a less selective inhibitor, it is unclear whether it would cause similar impairments.

Traumatic brain injury: Potential benefit (preclinical)

Ibudilast reduces glial activation in the context of CNS injury. The level of benefit is expected to relate to the nature of the neurological injury, and the extent to which glial activation contributes to pathology.

In a rat model of traumatic brain injury, treatment with ibudilast (10 mg/kg, subcutaneous) before and after injury prevented both the induction of an anxiety-like phenotype of enhanced freezing behavior

and the injury-related increase in reactive astrocytes and microglia in the hippocampus and amygdala [27]. Ibudilast also progressively ameliorated this anxiety-like behavior over the course of 6 months, when administered starting 1 month after injury [28]. The resolution of this behavioral phenotype was accompanied by a decrease in reactive glia, suggesting that chronic aberrant glial activation may be key drivers in brain-injury induced anxiety, such as post-traumatic stress disorder.

Stroke: Potential benefit (preclinical)

In preclinical models, high-dose ibudilast has been shown to mitigate inflammation-associated neuropathology when administered close to the time of injury. Although ibudilast has been used for over 20 years in stroke patients to alleviate vertigo, it has not been established whether its use leads to an improvement in long-term neurological outcomes, or a decrease in the incidence of vascular dementia. Since the dose used for this indication (30 mg/day) is lower than what has been found to be required for neuroprotection in neurodegenerative diseases (60-100 mg/day), it is unclear whether potential benefits would be apparent at the lower dose.

Ibudilast was also found to **mitigate pathology associated with impaired blood flow to the brain**. In a male rat model of chronic cerebral hypoperfusion, ibudilast (60 mg/kg orally) reduced the formation of cerebrovascular white matter lesions by 50-70% ($P<0.001$), and decreased levels of $TNF\alpha^+$ reactive glia [29]. These white matter lesions are commonly found in patients with vascular dementia, and associated with cognitive impairment [30]. Notably, ibudilast was ineffective at lower doses; in clinical studies neuroprotective effects were also only demonstrated at high doses, suggesting a threshold effect for CNS-associated benefits.

Ibudilast was also **protective only at high dose** (60 mg/kg) in a female rat model of cerebral aneurysm. This was associated with a reduction in endothelial PDE4, and reduced migration of macrophages into the vascular wall, due to decreased expression of cell-adhesion molecules (MMP-9, ICAM-1, VCAM-1, P-selectin) [31]. The authors note that due to its anti-platelet effects, ibudilast may only be a feasible treatment option for stroke patients also requiring anti-thrombotic therapy.

Ibudilast (10mg/kg i.v.) reduced infarct size by 40%, reduced brain edema by 55-88%, and improved neurological outcomes in the MCAO male rat stroke model [32]. However, the study found that ibudilast had a narrow therapeutic window, up to 2 hours following stroke onset, making it unclear whether it would have much acute clinical efficacy in a real-world setting.

APOE4 interactions: *Unknown*

Aging and related health concerns: May benefit vascular health by improving circulation without affecting blood pressure or heart rate, though only a few small studies have been carried out in humans.

Types of evidence:

- 4 RCT (Phase 1: Headache n=34, Migraine n=33; Phase 2: Opioid dependence n=11, 31)
- 4 clinical studies (Controlled trials: Diabetic nephropathy n=16, Diabetic poor circulation n=41; Non-controlled: Diabetic retinopathy n=8, Diabetic neuropathy n=26)
- Numerous laboratory studies

Cardiovascular: Potential benefit (preclinical)

Due to its vasodilatory, platelet anti-aggregation effects, and anti-inflammatory effects, ibudilast is expected to improve circulation [33]. A few preclinical studies have indicated that ibudilast may protect the vasculature, but there have been no studies examining how treatment with ibudilast affects long-term cardiovascular health. Ibudilast was shown to **preferentially act as a vasodilator on cerebral blood vessels**, with 40-50X greater potency relative to peripheral arteries [34]. Based on *in vitro* models, the vessel relaxation is cAMP dependent and involves a decrease in cytosolic Ca^{2+} [34; 35]. In high-fat diet fed rabbits, hyperlipidemia leads to increased production of thromboxane and damage to vascular endothelial cells [36]. Ibudilast (10 mg/kg/day) was able to reduce atherosclerotic lesions in this model by reducing serum thromboxane levels, serum lipid peroxide levels, serum lipids, and CNS calcium concentrations. Notably, the **effects on vessel relaxation and blood flow occur independently of changes to systemic blood pressure**. In all clinical trials where it was measured, ibudilast did not affect systolic or diastolic blood pressure, or heart rate [8; 37; 38; 39; 40; 41].

Diabetes-related conditions: Potential minor benefit

High levels of blood glucose and inflammatory mediators can damage the vasculature and lead to poor circulation [42]. Reductions in blood circulation can then lead to damage in a variety of organ systems, and contribute to the development of diabetic retinopathy, neuropathy, and nephropathy. Based on its vasodilatory properties, ibudilast has been tested for its ability to improve circulation in diabetic patients and mitigate the expression of these diabetes-related conditions. Ibudilast has no direct effects on glycemic control [37].

A few small studies were conducted in the 1990s-early 2000s, but these were never followed-up with larger trials, and ibudilast was not further developed for these indications. Lower limb circulation, as

measured by increased cross-sectional area of the dorsal pedis artery was found to increase in Type 2 diabetic patients (n=41) in response to acute treatment with ibudilast (10 mg) (from 2.76 ±0.29 to 3.24 ±33 mm^2), but not with elastase, which is a protease used to lower cholesterol in the blood (2.76 ±0.25 to 2.59 ±0.18) [38]. Ibudilast (30 mg/day for 2 weeks) also improved mean circulation time in the retina relative to baseline (from 4.2 ± 2.8 to 3.0 ± 1.6 s; P= 0.0215) [39]. In diabetic patients with microalbuminuria (n=16), ibudilast (30 mg/day for 18 months) improved urinary albumin excretion (from 72 ± 20 mg/g Cr to 52 ± 19 mg/g Cr, vs. 99 ± 46 mg/g Cr in control), potentially indicating a benefit to kidney function [37]. Improvements in nerve conduction velocity were also noted in a study of patients (n=26) with diabetic neuropathy [43].

Neuropathy: Potential minor benefit

Preclinical studies have indicated that ibudilast may have anti-nociceptive effects, as it was shown to be beneficial in models of central and peripheral neuropathy [44; 45; 46; 47]. However, it is unclear how well these effects translate to humans, as results from clinical trials assessing analgesic-related measures have been inconsistent, and the benefits were relatively minor [48; 49; 50]. The discrepancy may be related to the timing of treatment relative to the induction of nerve damage. Ibudilast appears to be most effective when administered during the period when pathological inflammatory processes are being initiated.

In male rats with spinal cord injury, the level of reactive astrocytes was found to increase from days 3-21 after injury [45]. Intrathecal ibudilast was found to reduce allodynia during this period, but higher doses were required at the later time points. The reduction in pain was associated with reduced pro-inflammatory molecule secretion by reactive glia. Ibudilast (10 mg/kg i.p.) was also **protective against the development of pain hypersensitivity** in models of spinal cord and sciatic nerve injury in male rats when administered during the period that hypersensitivity first manifests in these models [44]. Since the effects lasted beyond the treatment period, it was hypothesized that ibudilast can prevent the induction of processes that manifest as decreased tolerance to painful stimuli. Evidence from clinical trials suggests that it may be less effective in the context of established pain. In opioid-dependent individuals, ibudilast showed evidence of being able to potentiate the analgesic effects of opioids, such as oxycodone, but the effects are not consistent across trials or across measures within a trial [49; 50]. Ibudilast was also found to be ineffective in reducing pain associated with migraine or headache [48; 51].

Consequently, ibudilast **may be most beneficial in preventing the induction of chemotherapy-associated neuropathy**. In female mice, administration of ibudilast (10 mg/kg i.p.) prior to the

chemotherapeutic agent paclitaxel prevented the induction of peripheral neuropathy at the sensory-motor level [47]. This effect was attributed to the ability of ibudilast to prevent the increase in calcium that induces downstream pain-related signaling cascades. Ibudilast (7.5 mg/kg) pretreatment was also effective in preventing the development of oxaliplatin-induced tactile allodynia and memory impairments [46]. Whether cancer patients will derive a similar benefit will be tested in an upcoming clinical trial (NCT03782415).

Glaucoma: Potential benefit (preclinical)

A role for glial dysregulation and activation in the development and progression of glaucoma has been characterized in recent years [52]. In a rat model of high ocular pressure induced glaucoma, intraocular injection of ibudilast (500 μM) decreased the number of reactive GFAP$^+$ astrocytes/Muller glia and Iba1$^+$ CD68$^+$ microglia in both the retina and optic nerve [53]. It also decreased levels of proinflammatory cytokines (IL-1β, TNFα, IL-6, and MIF). Ibudilast **improved survival of retinal ganglion cells** (RGC) in the retina (92%: 1884 ± 44 RGC/mm^2 vs 68%: 1399 ± 128), as well as their axons in the optic nerve (91%: 90,640 ± 2658 axons/nerve vs 61%: 61,319 ± 8112). These neuroprotective effects were dependent on cAMP accumulation in glia and PKA activation. Notably, these improvements occurred without a reduction in ocular pressure, suggesting that ibudilast targets the processes underlying high pressure-induced RGC neurodegeneration.

Although ibudilast is available in ophthalmic formulation (Ketas® Eye-drops 0.01%) for eye allergies, it has not yet been examined whether the use of these drops alters the risk for glaucoma or other degenerative eye diseases.

Safety: Low-dose ibudilast has good long-term safety profile. Nausea and gastrointestinal symptoms are primary side effects. Short-term safety profile of high-dose treatment is similar to low-dose, but the long-term effects have not been established.

Types of evidence:

- 10 RCT (Phase 1: Healthy volunteers n=18 Alcohol dependence n=24, Methamphetamine dependence n=11, Headache n=34, Migraine n=33; Phase 2: Methamphetamine dependence n=140(est.), Opioid dependence n=11, 31, RRMS n=297, Progressive MS n=255, ALS n=108), Post-stroke dizziness (n=238, n=937)
- 2 controlled clinical trials (Diabetic nephropathy n=16, Diabetic poor circulation n=41)
- Post-marketing safety for Ketas® in Asthma and Post-stroke dizziness (n=14, 968)

- Numerous laboratory studies

Ibudilast has a **good safety profile** based on use for approximately 30 years for asthma and post-stroke dizziness. Ibudilast is metabolized in the liver into dihydroxy-ibudilast, and based on a Phase 1 study, peak plasma levels occur at 4 hours, and 60% of the drug is eliminated in the urine within 72 hours of intake [54]. Due to its liver-based metabolism, elderly individuals with liver hypofunction may experience elevated plasma drug levels (Ketas® product insert). According to the product insert for Ketas®, adverse events have been reported in 3.39% of approximately 15,000 users. The most common reported adverse events are anorexia, nausea, and increase in liver enzymes. Rare instances of thrombocytopenia and hepatic dysfunction have been reported, and it is recommended that the drug be discontinued if these occur. In large clinical studies in stroke patients, the primary adverse event was gastrointestinal related symptoms (11.2% in n=238 RCT, and 2.3% in n=937 study) [55; 56].

In clinical trials using higher doses (40-100 mg), ibudilast continued to be well-tolerated, and in most studies the rate of overall adverse events was similar between ibudilast and placebo groups [5; 8; 14; 40; 41; 48; 51]. The **most common adverse events were gastrointestinal symptoms, primarily nausea, and headache**. While ibudilast has **not been shown to have a strong emetic effect** at the doses used in these studies, some people may be particularly sensitive to its effects, as 2 healthy volunteers in a Phase 1 safety study had to withdraw due to vomiting [54]. Ibudilast does not affect blood pressure or heart rate [8; 37; 38; 39; 40; 41]. The maximum tolerated dose has not been established.

In addiction studies, there were no adverse drug-drug interactions with ibudilast and drugs of abuse (alcohol, opioids, methamphetamine) [8; 40; 41]. Due to its anti-platelet effects, ibudilast is expected to have drug-interactions with other anti-coagulants (Drugbank.ca).

Sources and dosing:

Ibudilast is marketed and available by prescription in Japan and Korea by Kyorin Pharmaceutical under the brand name Ketas®, and the generic version called Pinatos, from Taisho Yakuhin (Drugs.com). It is available in 10 mg delayed-release capsules taken orally. The recommended dose for asthma is 20 mg/day, and the recommended dose for post-stroke dizziness is 30 mg/day. Ibudilast is also available in an ophthalmic formulation (eye drops) as Ketas 0.1% from Kyorin Pharmaceutical and Eyevinal 0.1% from MSD (Drugs.com).

Recent clinical trials for CNS-associated diseases have been sponsored by MedicNova and use their 10 mg delayed release capsule formulation (MN-166). Higher doses (60-100 mg/day) have been necessary

to produce sustained effects in the CNS. The optimal dose for neurodegenerative diseases has not yet been established.

Research underway:

According to Clinicaltrials.gov, there are currently 5 active trials. There are two Phase 2 trials in people with alcohol abuse disorder for reduction of alcohol consumption (NCT03594435), and mitigation of withdrawal-induced dysphoria (NCT03489850), respectively. It is being tested in a Phase 1/2 trial for the prevention or mitigation of chemotherapy (Temozolomide) induced neuropathy in glioblastoma patients (NCT03782415).

There are also two imaging-based studies aimed at assessing how ibudilast affects brain neuroinflammation. These studies involve use of the PET ligand [11C]-PBR28 in ALS patients (NCT02714036), and MRS, MRI, and PET imaging in methamphetamine users (NCT03341078). These studies will be important for determining whether ibudilast significantly reduces brain inflammation at clinically used doses, and could be a relevant biomarker in determining therapeutic response.

Search terms:

Pubmed, Google: Ibudilast or AV-411 or MN-166 +

Alzheimer's diease, dementia, neurodegeneration, stroke, aging, cardiovascular, diabetes, addiction, inflammation, microglia, clinical trials, safety

Websites visited for Ibudilast:

- Clinicaltrials.gov
- Drugs.com
- PubChem
- DrugBank.ca
- Patientslikeme.com
- Cafepharma

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