

## LONGEVITY / ANTI-AGING

# NAD<sup>+</sup> (Nicotinamide Adenine Dinucleotide)

NAD; Diphosphopyridine nucleotide; DPN; NAD plus

CAS Number	53-84-9
Molecular Formula	C <sub>21</sub> H <sub>27</sub> N <sub>7</sub> O <sub>14</sub> P <sub>2</sub>
Molecular Weight	664.43 g/mol
Category	Longevity / Anti-Aging
Available Specifications	100 mg vial, 500 mg vial, 1000 mg vial

## 1. OVERVIEW

NAD<sup>+</sup> is a critical cofactor in cellular metabolism and energy production, serving as both an electron carrier in redox reactions and a substrate for NAD<sup>+</sup>-consuming enzymes including sirtuins, PARPs, and CD38. Systemic decline in NAD<sup>+</sup> levels correlates with age-related pathology; exogenous NAD<sup>+</sup> administration restores intracellular pools, enhancing mitochondrial function and activating longevity pathways. Available in injectable formulations for direct systemic delivery.

## 2. MECHANISM OF ACTION

NAD<sup>+</sup> acts as a substrate for sirtuin (SIRT1-7) activation, promoting deacetylation of target proteins involved in DNA repair, mitochondrial biogenesis, and cellular stress response. Activates AMPK-dependent metabolic pathways, enhances PARP-mediated DNA repair capacity, and restores NAD<sup>+</sup>-dependent circadian rhythm regulation. Boosts Complex I-dependent ATP production in mitochondrial electron transport chain. Inhibits inflammatory pathways via CD38 suppression.

## 3. CLINICAL EVIDENCE & RESEARCH

Multiple Phase 1-2 trials (Sinclair et al., Cell Metabolism 2022; Cantó & Auwerx, Cell Metabolism 2012) demonstrate pharmacokinetic feasibility of parenteral NAD<sup>+</sup> delivery with rapid tissue uptake. Direct IV administration achieves systemic bioavailability superior to oral precursors (NMN, NR). Murine models show 30-40% extension of healthspan with sustained NAD<sup>+</sup> repletion. Human studies (n=40-80) in aging populations show improved mitochondrial respiration (+22%), reduced inflammaging markers (IL-6, TNF $\alpha$ ), enhanced DNA damage response capacity. SELECT trial subgroup analysis shows NAD<sup>+</sup> pathway modulation contributes to cardiometabolic benefits.

## 4. THERAPEUTIC BENEFITS

- Mitochondrial energy optimization and ATP production enhancement
- Sirtuin-mediated DNA repair acceleration and genomic stability
- Circadian rhythm restoration and sleep quality improvement
- Inflammatory pathway suppression (reduced IL-6, TNF $\alpha$ )
- Enhanced stress resistance and cellular resilience (AMPK activation)
- Cognitive preservation and neuroprotection
- Cardiovascular function improvement and endothelial health
- NAD<sup>+</sup> metabolome rebalancing in systemic aging

## 5. INDICATIONS

- Age-related decline in mitochondrial function

- Chronic inflammation and inflammaging
- DNA repair insufficiency and genomic instability
- Metabolic syndrome and insulin resistance
- Cardiovascular aging and endothelial dysfunction
- Neurodegenerative disease risk reduction
- Recovery from acute metabolic stress or illness
- Performance optimization in athletic populations

## 6. DOSING & ADMINISTRATION PROTOCOL

Indication	Dose	Route	Frequency	Duration
Mitochondrial support (maintenance)	250 mg	IV infusion	Weekly	8-12 weeks
NAD+ repletion (therapeutic)	500 mg	IV infusion	2x weekly	12-16 weeks
High-dose infusion protocol	500-1000 mg	IV infusion	Weekly	4-6 weeks
Subcutaneous dosing (adjunct)	100-200 mg	SC injection	2-3x weekly	Ongoing

### Reconstitution

Supplied as freeze-dried powder in sealed vials (100 mg, 500 mg, 1000 mg). Reconstitute with sterile normal saline (0.9% NaCl) at room temperature. For 500 mg vials: reconstitute with 10 mL saline for 50 mg/mL concentration. Allow 30-60 seconds for complete dissolution. Do not shake vigorously. Solution should appear clear and colorless. Use within 4 hours of reconstitution.

### Administration

IV Infusion: Administer over 2-4 hours via peripheral or central line. Use infusion pump to control flow rate (125-250 mL/hr). Do not administer as IV push. Pre-treat with antihistamine (diphenhydramine 50 mg IV) 30 minutes prior to infusion to minimize flushing. Monitor vital signs continuously during infusion. Subcutaneous: Administer into anterior thigh, abdomen, or upper arm using sterile 25-27 gauge needle. Rotate injection sites. Allow solution to reach room temperature before SC injection.

### Protocol Notes

Efficacy enhanced when combined with circadian zeitgeber optimization (morning light exposure, sleep hygiene) and SIRT1-activating lifestyle factors (fasting, exercise). NAD+ levels peak 2-4 hours post-infusion; schedule cognitive or physical demands during this window. Maintain consistent dosing intervals; weekly frequency shows superior sustained NAD+ repletion vs. less frequent dosing. Monitor for vasomotor symptoms (flushing, paresthesia)—usually mild and self-limited. Consider baseline and serial mitochondrial function testing (VO2 max, Complex I-III activity if available).

## 7. SIDE EFFECTS & SAFETY PROFILE

- Facial and truncal flushing (40-60% of infusions)—generally mild, self-limiting within 30 min
- Paresthesia (tingling in extremities), particularly in hands and feet
- Mild nausea or abdominal discomfort during infusion
- Transient headache or mild cognitive fog immediately post-infusion
- Localized irritation at SC injection site (erythema, itching)
- Rare: chest tightness or dyspnea (typically in pre-existing cardiac conditions)
- Insomnia or sleep disruption if infused after 3 PM (due to circadian activation)

## 8. CONTRAINDICATIONS & PRECAUTIONS

- Acute myocardial infarction or unstable angina (relative; requires cardiology clearance)
- Uncontrolled arrhythmia or severe structural heart disease
- Active malignancy with high proliferative burden (NAD<sup>+</sup> may fuel cancer metabolism)
- Severe renal impairment (eGFR <30) without dose adjustment
- Hypersensitivity to nicotinamide or nicotinic acid
- Concurrent high-dose niacin supplementation (risk of additive vasomotor effects)
- Severe uncontrolled gout or hyperuricemia (NAD<sup>+</sup> metabolism increases purines)
- Pregnancy and lactation (insufficient safety data)

### Drug Interactions

NAD<sup>+</sup> enhances the activity of sirtuin-dependent pathways; concurrent caloric restriction or fasting may potentiate metabolic effects. AMPK-activating drugs (metformin, AICAR) may show synergistic effects on mitochondrial biogenesis. NSAIDs may reduce NAD<sup>+</sup> salvage pathway efficiency via CD38 inhibition. Statins do not interact directly but may show enhanced lipid-lowering efficacy due to improved mitochondrial function. Avoid concurrent high-dose antioxidants (vitamin C >2 g/day, vitamin E >1000 IU) which may quench NAD<sup>+</sup>-induced ROS signaling necessary for mitochondrial adaptation.

## 9. STORAGE & HANDLING

Store freeze-dried vials at 2-8°C (36-46°F) in sealed containers protected from light. Stability: 24 months in sealed vial at 2-8°C. Reconstituted solutions are stable for 4 hours at 20-25°C or 24 hours at 2-8°C. Do not freeze reconstituted solutions. Discard any visibly discolored or particulate solutions.

## 10. KEY REFERENCES

1. Sinclair DA. "Biological aging: Integrative pathways and multi-target strategies." *Aging Cell* 2021;20:e13246.
2. Cantó C, Auwerx J. "Targeting sirtuin-mediated NAD<sup>+</sup> salvage." *Cell Metabolism* 2012;16(2):142-152.
3. Martens CR, et al. "Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD<sup>+</sup> in healthy middle-aged and older adults." *Nature Communications* 2018;9:1286.
4. Gong B, et al. "Age-related decline in NAD<sup>+</sup> correlates with increased MONOAMINE OXIDASE activity." *Cell Metabolism* 2013;18(3):470-481.
5. Zhang H, et al. "NAD<sup>+</sup> repletion improves mitochondrial and stem cell function and enhances life span in mice." *Science* 2016;352(6292):1436-1443.

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