



**Hinz Medical Foods™ / NeuroResearch Centers, Inc.™**

1150 88<sup>th</sup> Ave. West - Duluth, MN +1-218-626-2220 | [www.HinzMedicalFoods.com](http://www.HinzMedicalFoods.com)

**Hypo-serotonergic™ conditions** occur when serotonin concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a modified normal diet.™

**Hypo-dopaminergic™ conditions** occur when dopamine concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a modified normal diet.™

**Hypo-glutathionemia™ conditions** occur when glutathione concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a modified normal diet.™

- Giving only *serotonin precursors* can deplete dopamine and glutathione.™
- Giving only *dopamine precursors* can deplete serotonin and glutathione.™
- Giving only *glutathione or glutathione precursors* can deplete serotonin and dopamine.™

The centrally acting monoamines (monoamines) are serotonin, dopamine, norepinephrine, and epinephrine.

For the management of **hypodopaminergic™ conditions or states** that may accompany

## Parkinson's disease

A **hypodopaminergic** condition or state often accompanies Parkinson's disease (see the right column).

After diagnosing Parkinson's disease, formulate a differential diagnosis to rule out accompanying issues, including a **hypodopaminergic** condition or state.

Identify the presence of a **hypodopaminergic** condition or state with an empirical trial of the **hypodopaminergic** condition or state protocol (see page 2).

Mucuna Medical Food™ is for the Management of **hypodopaminergic** conditions or states which may display symptoms that require establishing dopamine concentrations higher than are possible with modification of the normal diet.

In this case (Parkinson's disease), the **hypodopaminergic** state would be associated with decreased cortical physiological efficiency in information processing; that is, a larger neuronal pool may be required to carry out the task in the dopamine depleted state than during the dopamine-replete state.

Mattay, V. et al. Dopaminergic Modulation of Cortical Function in Patients with Parkinson's Disease Ann Neurol 2002;51:156-164

**Hypodopaminergic** states are hypothesized to be associated with apathy, depression, and anxiety.

Getz, S. et al. Cognitive and Neuropsychiatric Features of Early Parkinson's Disease Archives of Clinical Neuropsychology 32 (2017) 769-785

The imaging data revealed a robust bilateral amygdala response in NCs (normal controls) that was absent in PD (Parkinson's disease) patients during the **hypodopaminergic state**. Tessitore A., et al. Dopamine Modulates the Response of the Human Amygdala: A Study in Parkinson's Disease J of Neuroscience, October 15, 2002, 22(20):9099-9103

In this case, the **hypodopaminergic** state would be associated with decreased cortical physiological efficiency in information processing; that is, a larger neuronal pool may be required to carry out the task in the dopamine depleted state than during the dopamine-replete state.

Mattay, V. et al. Dopaminergic Modulation of Cortical Function in Patients with Parkinson's Disease Ann Neurol 2002;51:156-164

### Mucuna Medical Food™

Active ingredient L-dopa

For the management of **hypodopaminergic** conditions that may accompany Parkinson's disease and cannot be addressed with modification of the normal diet (Note: not indicated for Parkinson's disease).



**R&R™ Medical Food** is for managing **hypo-serotonergic** conditions that may accompany Parkinson's disease and cannot be addressed with modification of the normal diet.

**TO ORDER FOR THE CLINIC, PHARMACY, OR INITIATE PATIENT ONLINE ORDERING CONTACT NEURORESEARCH CENTERS +1-218-626-2220 1150 88TH AVE W, DULUTH, MN | [BRENDA@NEUROASSIST.COM](mailto:BRENDA@NEUROASSIST.COM)** Mucuna Medical Food and R&R are medical food administered enterally under the supervision of a healthcare professional for the specific dietary management of **hypodopaminergic** or **hypo-serotonergic** conditions or states.



**Description:**

The hypodopaminergic conditions or states can occur when systemic dopamine concentrations on a normal diet are not enough, low, inadequate, depleted, deficient, deficit, or suboptimal.

Mucuna Medical Food™ (MMF™) is a specially formulated and processed medical food not available as a naturally occurring foodstuff for patients with a hypodopaminergic condition. MMF powder™ can achieve systemic dopamine concentrations higher than normal diets. MMF powder is for the partial feeding of a patient via a powder taken orally. The ingredients in MMF powder are for administration in a daily dosing range determined by medical evaluation. R&R™ is a specially formulated static dosed (one size fits all) medical food. Concomitant administration of R&R with MMF powder is needed to address the ability of MMF powder to induce hyposerotonergic and glutathionemia conditions. R&R also provides the necessary cofactors to address relative nutritional deficiencies associated with hypodopaminergic, hyposerotonergic, and glutathionemia conditions.<sup>1,2,3,4,5,6,7,8,9,10,11,12</sup>

**Intended Use:**

The formulation of MMF powder is a medical food administered enterally under a healthcare professional's supervision for hypodopaminergic conditions or states' specific dietary management.

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<sup>1</sup> Stansley B. et al. L-Dopa and Brain Serotonin System Dysfunction *Toxics* 2015, 3, 75-88; doi:10.3390/toxics3010075

<sup>2</sup> Miguez C. et al. Impairment of Serotonergic Transmission by the Antiparkinsonian Drug L-DOPA: Mechanisms and Clinical Implications *Frontiers in Cellular Neuroscience* Vol 11 Article 274 1-7 Sep. 2017

<sup>3</sup> Ritvo E. et al. Effects of L-dopa in autism *Journal of Autism and Developmental Disorders* Volume 1, Number 2 / June, 1971 190-205

<sup>4</sup> Omenn GS, Smith LT. A common uptake system for serotonin and dopamine in human platelets. *J Clin Invest.* 1978 Aug;62(2):235-40. doi: 10.1172/JCI109121. PMID: 670392; PMCID: PMC371758.

<sup>5</sup> Blau N, Thöny B, Cotton RG, Hyland K. Disorders of tetrahydrobiopterin and related biogenic amines. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler K, Vogelstein B, editors. *The Metabolic and Molecular Bases of Inherited Disease*. 8. New York: McGraw-Hill; 2001. pp. 1725–1776.

<sup>6</sup> McInnes RR, Kaufman S, Warsh JJ, Van Loon GR, Milstien S, Kapatoss G, Soldin S, Walsh P, MacGregor D, Hanley WB. Biopterin synthesis defect. Treatment with L-dopa and 5-hydroxytryptophan compared with therapy with a tetrahydropterin. *J Clin Invest.* 1984 Feb;73(2):458-69. doi: 10.1172/JCI11232. PMID: 6142058; PMCID: PMC425037.

<sup>7</sup> University of Wisconsin Chemistry Department. Competitive Inhibition definition. Available at <https://www2.chem.wisc.edu/deptfiles/genchem/netorial/modules/biomolecules/modules/enzymes/enzyme5.htm>

<sup>8</sup> ScienceDirect. Competitive inhibition article. Available at <https://www.sciencedirect.com/topics/neuroscience/competitive-inhibition>.

<sup>9</sup> Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. Glutathione dysregulation and the etiology and progression of human diseases. *Biol Chem.* 2009 Mar;390(3):191-214. doi: 10.1515/BC.2009.033. PMID: 19166318; PMCID: PMC2756154.

<sup>10</sup> Wu Z, Dryhurst G. 7-S-Glutathionyltryptophan-4,5-dione: Formation from 5-Hydroxytryptophan and Reactions with Glutathione. *Bioorganic Chemistry.* 1996 Jun;24(2):127-149. <https://doi.org/10.1006/bioo.1996.0012>.

<sup>11</sup> Dagnino-Subiabre A, Cassels BK, Baez S, Johansson AS, Mannervik B, Segura-Aguilar J. Glutathione transferase M2-2 catalyzes conjugation of dopamine and dopa o-quinones. *Biochem Biophys Res Commun.* 2000 Jul 21;274(1):32-6. doi: 10.1006/bbrc.2000.3087. PMID: 10903891.

<sup>12</sup> Kato Y, Peskin AV, Dickerhof N, Harwood DT, Kettle AJ. Myeloperoxidase catalyzes the conjugation of serotonin to thiols via free radicals and tryptamine-4,5-dione. *Chem Res Toxicol.* 2012 Nov 19;25(11):2322-32. doi: 10.1021/tx300218f. Epub 2012 Oct 10. PMID: 23009681.



## Mucuna Medical Food™ Powder Product Insert

Examples of hypodopaminergic condition etiologies faced by patients on a normal diet include but are not limited to nutrient-induced competitive inhibition depletion at the aromatic amino acid enzyme<sup>13,14</sup>; drug-induced dopamine depletion<sup>15</sup>; aromatic amino acid decarboxylase deficiency<sup>16</sup>; tetrahydrobiopterin (BH4) deficiency<sup>17</sup>; age-related suboptimal dopamine concentrations<sup>18</sup>; dysfunction of dopamine regulated transporter function or decrease in dopamine transporter activity<sup>19</sup>; loss of dopaminergic neurons<sup>20</sup>; disease-associated low dopamine idiopathic etiology; low dopamine associated with Parkinson's disease<sup>21</sup>; dopamine associated post-traumatic stress disorder<sup>22</sup>; dopamine-related suicide risk<sup>23</sup>; bipolar type 1 associated low dopamine;<sup>24</sup> dopamine-related depression;<sup>25</sup> and low dopamine related to ADHD<sup>26</sup>

## DOSAGE, ADMINISTRATION, INGREDIENTS

**NOTICE: THIS PRODUCT'S INTENDED USE OCCURS ONLY UNDER THE DIRECT SUPERVISION OF A PHYSICIAN OR OTHER LICENSED HEALTHCARE PRACTITIONER.**

### Dosing

The recommended starting dose of MMF powder is 2.4 grams in three divided daily doses. Based on medical evaluation, the caregiver may increase MMF powder's daily dosing weekly by 1.8 grams or 2.4 grams per day to achieve the optimal dose for control of hypodopaminergic condition symptoms. Weekly evaluation via in-office visits or telemedicine is associated with optimal results. Optimal control of hypodopaminergic conditions may occur in one week or may require many weekly visits as determined by medical evaluation. Concomitant administration of MMF powder with R&R is needed as one tablet twice a day to provide cofactors and address the ability of MMF powder to

<sup>13</sup> Stansley, B., Yamamoto B. L-Dopa and Brain Serotonin System Dysfunction Toxics 2015, 3, 75-88.

<sup>14</sup> Garcia N. et al. Chronic oral L-DOPA increases dopamine and decreases serotonin excretions Am J Physiol Regulatory Integrative Comp Physiol 277:1476-1480, 1999.

<sup>15</sup> Lam R. et al. Effects of Alpha-Methyl-Para-Tyrosine-Induced Catecholamine Depletion in Patients with Seasonal Affective Disorder in Summer Remission NEUROPSYCHOPHARMACOLOGY 2001 VOL 25 NO S5

<sup>16</sup> Hyland K., Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids Journal of Nutrition, Volume 137, Issue 6, June 2007, Pages 1568S-1572S.

<sup>17</sup> Federal Register Vol. 84, No. 130 July 8, 2019 p. 32268.

<sup>18</sup> Rutledge R. et al. Risk Taking for Potential Reward Decreases across the Lifespan Current Biology 26, 1634-1639, June 20, 2016

<sup>19</sup> Vaughn R. et al. Mechanisms of dopamine transporter regulation in normal and disease states Trends Pharmacol Sci. 2013 September ; 34(9)

<sup>20</sup> Segura-Aguilar J. On the role of endogenous neurotoxins and neuroprotection in Parkinson's disease. Neural Regen Res. 2017;12(6):897-901. doi:10.4103/1673-5374.208560

<sup>21</sup> Kish S. et al. Brain dopamine neurone 'damage': methamphetamine users vs. Parkinson's disease—a critical assessment of the evidence European Journal of Neuroscience, Vol. 45, pp. 58-66

<sup>22</sup> Drury S. et al. The Role of the Dopamine Transporter (DAT) in the Development of PTSD in Preschool Children J Trauma Stress. 2009 December ; 22(6): 534-539. doi:10.1002/jts.20475.

<sup>23</sup> Rydning E. et al. The role of dopamine and serotonin in suicidal behaviour and aggression Progress in Brain Research Volume 172, 2008, Pages 307-315

<sup>24</sup> Moriera T. et al. Impulse control loss rapidly reversed by aripiprazole in a patient with concomitant bipolar disease type I and posttraumatic frontal lobe lesions BMJ Case Reports 2011; doi:10.1136/bcr.09.2011.4756

<sup>25</sup> Belujon P. et al. Dopamine System Dysregulation in Major Depressive Disorders International Journal of Neuropsychopharmacology (2017) 20(12): 1036-1046

<sup>26</sup> Barone H. et al. Tyrosinemia Type 1 and symptoms of ADHD: Biochemical mechanisms and implications for treatment and prognosis Am J Med Genet.2020;183B:95-105



## Mucuna Medical Food™ Powder Product Insert

induce hyposerotonergic and glutathionemia conditions. Caregiver adjustment of the R&R daily dosing may be needed if side effects caused by serotonin-dopamine imbalance develop. Administering greater than three pills of R&R per day for side effect management is not recommended.

### **Ingredients**

MMF powder is a white mucuna pruriens powder that requires weighing the daily dosing value on a weight scale with a minimum of 0.01 gram (one-one hundredth of a gram) accuracy. Active ingredients include:

- Mucuna Pruriens (active ingredient 40% L-dopa)

### **Discontinuation of MMF**

There are no known adverse events or reactions associated with the abrupt stopping of MMF powder.

### **CONTRAINDICATIONS**

Administering MMF powder to patients with known hypersensitivity is contraindicated.

### **PREGNANCY**

No studies demonstrate the active ingredients in MMF powder cause pregnancy problems or are safe.

### **WARNINGS AND PRECAUTIONS**

#### **Renal or hepatic impairment**

There has been no documented elevation of renal or hepatic enzymes attributed to the nutrients found in MMF powder.

#### **ADVERSE REACTIONS**

This nutritional combination's side effects are nausea, vomiting, loss of appetite, lightheadedness, lowered blood pressure, confusion, and dyskinesia,<sup>27</sup>

#### **Drug Interactions**

The medical food MMF powder can increase systemic dopamine concentrations beyond the ability of the normal diet. As can occur at any point during drug administration, a side effect may occur.

#### **OVERDOSE**

Overdose symptoms may include diarrhea, weakness, and nausea. Should poisoning concerns arise, contact the local poison control.

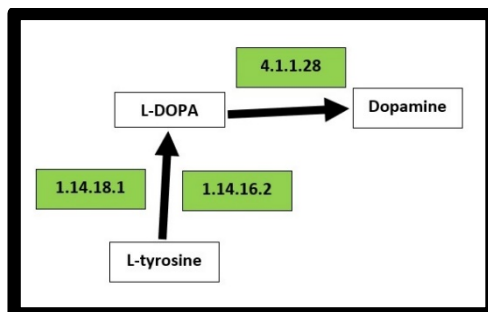
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<sup>27</sup> L-dopa side effects, Parkinson Organization Website, <https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Levodopa>



## CLINICAL PHARMACOLOGY

When a hypodopaminergic condition exists on a normal diet, dietary modification is not effective. Management of the hypodopaminergic condition while on a normal diet requires the immediate aromatic amino acid precursor of dopamine (mucuna pruriens active ingredient L-dopa) and vitamin B6, which activates AADC (EC 4.1.1.28).<sup>28</sup>



**Figure 1:** On a normal diet, the synthesis of L-dopa, the precursor of dopamine, is dependent on L-tyrosine.<sup>29</sup> Metabolism of L-tyrosine to L-dopa is rate limited by the tyrosine hydroxylase enzyme. No matter how great the L-tyrosine dosage is, there is a hard limit to dopamine synthesized. Metabolism of L-dopa to dopamine is without regulation. L-dopa administration can increase dopamine concentrations above concentrations achieved with L-tyrosine or L-phenylalanine from the normal diet.

As highlighted in Figure 1, the optimal activation of AADC (EC 4.1.1.28) depends on pyridoxine's (PLP, vitamin B6) adequate availability. The metabolism of L-tyrosine by tyrosine hydroxylase (EC 1.14.16.2) is rate limited. See Figure 1. No matter how much L-tyrosine is in the normal diet, there is a maximum limit to the amount of dopamine the body can synthesize from L-tyrosine. On a normal diet, L-dopa is a transient intermediate between L-tyrosine and dopamine, which is typically not found in substantial systemic concentrations or significant amounts in the normal diet, even with increasing intake of L-tyrosine containing foods. When the dopamine concentrations required by the body are higher than can be established on a normal diet, because of tyrosine hydroxylase rate-limitation, a hypodopaminergic condition exists.<sup>30,31,32,33</sup>

Increases in 5-HTP, L-dopa, serotonin, or dopamine may induce or exacerbate a glutathionemia caused by a glutathione-related RND on a normal diet. The special

<sup>28</sup> EC 4.1.1.28.

<sup>29</sup> Kyoto Encyclopedia of Genes and Genomes. Tyrosine metabolism - Homo sapiens (human). Available at: [https://www.genome.jp/kegg-bin/show\\_pathway?hsa00350](https://www.genome.jp/kegg-bin/show_pathway?hsa00350)

<sup>30</sup> Brun L, Ngu LH, Keng WT, Ch'ng GS, Choy YS, Hwu WL, Lee WT, Willemsen MA, Verbeek MM, Wassenberg T, Régál L, Orcesi S, Tonduti D, Accorsi P, Testard H, Abdenur JE, Tay S, Allen GF, Heales S, Kern I, Kato M, Burlina A, Manegold C, Hoffmann GF, Blau N. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. *Neurology*. 2010 Jul 6;75(1):64-71. doi: 10.1212/WNL.0b013e3181e620ae. Epub 2010 May 26. Erratum in: *Neurology*. 2010 Aug 10;75(6):576. Dosage error in article text. PMID: 20505134.

<sup>31</sup> Di Salvo ML, Fesko K, Phillips RS, Contestabile R. Editorial: PLP-Dependent Enzymes: Extraordinary Versatile Catalysts and Ideal Biotechnological Tools for the Production of Unnatural Amino Acids and Related Compounds. *Front Bioeng Biotechnol*. 2020 Feb 11;8:52. doi: 10.3389/fbioe.2020.00052. PMID: 32117932; PMCID: PMC7026007.

<sup>32</sup> Di Salvo ML, Fesko K, Phillips RS, Contestabile R. Editorial: PLP-Dependent Enzymes: Extraordinary Versatile Catalysts and Ideal Biotechnological Tools for the Production of Unnatural Amino Acids and Related Compounds. *Front Bioeng Biotechnol*. 2020 Feb 11;8:52. doi: 10.3389/fbioe.2020.00052. PMID: 32117932; PMCID: PMC7026007.

<sup>33</sup> Knappskog P. et al. Recessively inherited L-DOPA-responsive dystonia caused by a point mutation (Q381K) in the tyrosine hydroxylase gene *Human Molecular Genetics*, 1995, Vol. 4, No. 7 1209-1212



## Mucuna Medical Food™ Powder Product Insert

formulation of R&R addresses the specific static daily dosing needs of a nutrient-induced glutathionemia condition.<sup>35,36,37,38,39,40,41</sup>

### HOW SUPPLIED

MMF powder is in bottles of 90 pills (a one-month supply).

### STORAGE

Store MMF powder at room temperature; avoid storage in temperatures above 100 degrees Fahrenheit.

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<sup>35</sup> Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. Glutathione dysregulation and the etiology and progression of human diseases. *Biol Chem*. 2009 Mar;390(3):191-214. doi: 10.1515/BC.2009.033. PMID: 19166318; PMCID: PMC2756154. <https://pubmed.ncbi.nlm.nih.gov/19166318/>.

<sup>36</sup> Wu Z, Dryhurst G. 7-S-Glutathionyltryptophan-4,5-dione: Formation from 5-Hydroxytryptophan and Reactions with Glutathione. *Bioorganic Chemistry*. 1996 Jun;24(2):127-149. <https://doi.org/10.1006/bioo.1996.0012>.

<sup>37</sup> Spencer JP, Jenner P, Daniel SE, Lees AJ, Marsden DC, Halliwell B. Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. *J Neurochem*. 1998 Nov;71(5):2112-22. doi: 10.1046/j.1471-4159.1998.71052112.x. PMID: 9798937.

<sup>38</sup> Spencer JP, Jenner P, Halliwell B. Superoxide-dependent depletion of reduced glutathione by L-DOPA and dopamine. Relevance to Parkinson's disease. *Neuroreport*. 1995 Jul 31;6(11):1480-4. doi: 10.1097/00001756-199507310-00004. PMID: 7579129.

<sup>39</sup> Ritvo ER, Yuwiler A, Geller E, Kales A, Rashkis S, Schicor A, Plotkin S, Axelrod R, Howard C. Effects of L-dopa in autism. *J Autism Child Schizophr*. 1971 Apr-Jun;1(2):190-205. doi: 10.1007/BF01537957. PMID: 4335857.

<sup>40</sup> Benson R, Crowell B, Hill B, Doonquah K, Charlton C. The effects of L-dopa on the activity of methionine adenosyltransferase: relevance to L-dopa therapy and tolerance. *Neurochem Res*. 1993 Mar;18(3):325-30. doi: 10.1007/BF00969090. PMID: 8479601.

<sup>41</sup> Surtees R, Hyland K. L-3,4-dihydroxyphenylalanine (levodopa) lowers central nervous system S-adenosylmethionine concentrations in humans. *J Neurol Neurosurg Psychiatry*. 1990 Jul;53(7):569-72. doi: 10.1136/jnnp.53.7.569. PMID: 2391519; PMCID: PMC488131.

**Description:**

The etiology of hyposerotonergic conditions or states is when systemic serotonin concentrations on normal diet are not enough, low, inadequate, depleted, deficient, deficit, or suboptimal.

Administration of enteral R&R™ occurs under the supervision of a physician or other licensed caregiver for the dietary management of hyposerotonergic conditions or states, for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. The special formulation of R&R meets the distinctive nutritional requirements induced by hyposerotonergic conditions and states. The hyposerotonergic condition or state has an increased requirement for serotonin precursor 5-HTP or vitamin B6 to prevent serotonin-related symptoms or functional dysregulation. A modification of the normal diet cannot manage these unique nutritional requirements. The unique formulation of R&R provides necessary 5-HTP and vitamin B6 while being formulated to address the undesirable ability of aromatic amino acid precursors to induced hypodopaminergic or glutathionemia conditions or states.

**Intended Use:**

The formulation R&R is a medical food administered enterally under the supervision of a healthcare professional, for the specific dietary management of hyposerotonergic conditions or states.

Examples of hyposerotonergic condition etiologies while on a normal diet which may require R&R based on medical evaluation, to include but are not limited to: drug-induced serotonin depletion<sup>1,2,3,4,5</sup>, competitive inhibition serotonin depletion at the aromatic amino acid enzyme<sup>6,7</sup>, aromatic amino acid decarboxylase deficiency<sup>8</sup>, tetrahydrobiopterin (BH4) Deficiency<sup>9</sup>, genetic polymorphism G-T and G/A involving introne 6<sup>10</sup>, genetic serotonin transporter variance<sup>11</sup>, suboptimal serotonin concentrations, age-related serotonin suboptimal

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<sup>1</sup> Renoux C. et al. Association of Selective Serotonin Reuptake Inhibitors With the Risk for Spontaneous Intracranial Hemorrhage *AMA Neurol.* 2017;74(2):173-180

<sup>2</sup> Schultz J. et al. Serotonergic agents increase the incidence of gastrointestinal bleeds in patients with continuous-flow left ventricular assist devices. *International Society for Heart Transplantation*, 05 Jan 2016, 35(6):823-824

<sup>3</sup> Wagner A. et al. Effects of fluoxetine treatment of platelet 3H-imipramine binding, 5-HT uptake and 5-HT content in major depressive disorder *Journal of Affective Disorders* Volume 20, Issue 2, October 1990, Pages 101-113

<sup>4</sup> Maurer-Spurej E. et al. The influence of selective serotonin reuptake inhibitors on human platelet serotonin *Thromb Haemost* 2004; 91: 119-28

<sup>5</sup> Gagne, J. et al. Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting: A Cohort Study *Drug Safety* volume 38, pages1075–1082 (2015)

<sup>6</sup> Stansley, B., Yamamoto B. L-Dopa and Brain Serotonin System Dysfunction *Toxics* 2015, 3, 75-88

<sup>7</sup> Garcia N. et al. Chronic oral L-DOPA increases dopamine and decreases serotonin excretions *Am J Physiol Regulatory Integrative Comp Physiol* 277:1476-1480, 1999.

<sup>8</sup> Hyland K., Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids *Journal of Nutrition*, Volume 137, Issue 6, June 2007, Pages 1568S–1572S

<sup>9</sup> Federal Register Vol. 84, No. 130 July 8, 2019 p. 32268

<sup>10</sup> I. Paclt1, J. Koudelová, A. Křepelová, P. Uhlíková, M. Gazdíková & P. Bauer Biochemical markers and genetic research of ADHD *Neuroendocrinol Lett* 2005; 26(4):423–430

<sup>11</sup> Offenbaecher M. et al. Possible association of fibromyalgia with a polymorphism in the serotonin receptor gene regulatory region, *Arthritis & Rheumatism* Vol. 42, No. 11, November 1999, pp 2482–2488



## R&R™ Product Insert

serotonin concentrations<sup>12</sup>, decreased serotonin transporter activity<sup>13</sup>, increased numbers (and activity) of SERT (serotonin transporters) or a loss of serotonergic neurons<sup>14</sup>, low serotonin associated with Parkinson's disease<sup>15</sup>, low serotonin associated with Post-traumatic stress disorder<sup>16</sup>, low serotonin associated with chronic tension headache and migraine<sup>17</sup>, low serotonin associated with fibromyalgia<sup>18</sup>, and neurotoxin-induced hyposerotonergic condition<sup>19</sup>

## DOSAGE, ADMINISTRATION, INGREDIENTS

**NOTICE: THIS PRODUCT'S INTENDED USE OCCURS ONLY UNDER THE DIRECT SUPERVISION OF A PHYSICIAN OR OTHER LICENSED HEALTHCARE PRACTITIONER.**

### Dosing

Take as directed by your caregiver. The recommended adult daily dosing of R&R™ is two pills three times a day.

### Nausea

If nausea develops during the first week of the R&R™ administration, contact the prescribing caregiver. If nausea occurs when taking the first dose within one to two hours of waking, move the first dose of the day to noon (4 to 5 hours after waking).

### Ingredients

R&R is a white 1.9 cm non-scored round white pill with 2.948-grams of active ingredients.

Active ingredients includes:

- L-cysteine
- L-tyrosine
- Vitamin C (ascorbic acid)
- Mucuna Pruriens (active ingredient 40% L-dopa)
- 5-hydroxytryptophan
- Calcium citrate
- Vitamin B6 (pyridoxine hydrochloride)
- Folate
- Selenium

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<sup>12</sup> Nitkita L. et al. The impact of protein supplementation on cognitive performance in frail elderly Eur J Nutr 2014 Apr;53(3):803-12.

<sup>13</sup> Shih-Hsien L. et al. Serotonin and Mental Disorders: A Concise Review on Molecular Neuroimaging Evidence Clinical Psychopharmacology and Neuroscience 2014;12(3):196-202

<sup>14</sup> Hess S. et al. Advances in vivo imaging of serotonergic neurons in neuropsychiatric disorders Neuroscience and Biobehavioral Reviews 28 (2004) 547–563

<sup>15</sup> Tan S. et al. Serotonin-dependent depression in Parkinson's disease: A role for the subthalamic nucleus Neuropharmacology 61 (2011) 387e399

<sup>16</sup> DeBellis M. et al. Biologic Findings of Post-traumatic Stress Disorder and Child Maltreatment Current Psychiatry Reports 2003, 5:108–117

<sup>17</sup> Anthony, M. Plasma serotonin in patients with chronic tension headaches Journal of Neurology, Neurosurgery, and Psychiatry 1989;52:182-184

<sup>18</sup> Amin O. et al. Clinical association of vitamin D and serotonin levels among patients with fibromyalgia syndrome Neuropsychiatric Disease and Treatment 2019;15 1421–1426

<sup>19</sup> McCann U. et al. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings Lancet 1998; 352: 1433–37





**Discontinuation of R&R**

There are no known adverse events or reactions associated with the abrupt stopping of R&R.

**CONTRAINDICATIONS**

Administering R&R to patients with known hypersensitivity to any of the components contained in this product is contraindicated.

**PREGNANCY**

No studies demonstrate the active ingredients in R&R cause pregnancy problems or are safe.

**WARNINGS AND PRECAUTIONS**

**Renal or hepatic impairment**

There has been no documented elevation of renal or hepatic enzymes attributed to the nutrients found in R&R.

**ADVERSE REACTIONS**

Side effects for this nutritional combination is dry mouth, insomnia, headache, nausea, dizziness, constipation.

**Drug Interactions**

The medical food R&R is intended to increase systemic serotonin concentrations beyond the ability of the normal diet. As can occur at any point during drug administration, a side effect may occur.

**OVERDOSE**

Overdose symptoms may include diarrhea, weakness, and nausea. Should poisoning concerns arise, contact the local poison control.

**CLINICAL PHARMACOLOGY**

A relative nutritional deficiency occurs when a normal diet does not meet the needs of the system. When systemic serotonin concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a normal diet, the hyposerotonergic condition or state caused by a serotonin-related relative nutritional deficiency exists.

On a normal diet, L-tryptophan is the primary amino acid precursor metabolized to serotonin. A limitation of the amount of serotonin synthesized is regulated by the enzyme tryptophan hydroxylase, which restricts (limits) the metabolism of L-tryptophan to 5-hydroxytryptophan (5-HTP). When adequate cofactor (vitamin B6) activated enzyme concentrations exist, the only substance which can increase serotonin concentrations higher than can be achieved with L-tryptophan from the optimized normal diet is 5-HTP, the immediate amino acid precursor of

## R&R™ Product Insert



serotonin.<sup>20,21,22,23</sup>

The R&R medical food, through its special formulation, addresses the ability of 5-HTP to induce or exacerbate hypodopaminergic conditions (dopamine-related relative nutritional deficiency) secondary to competitive inhibition between immediate precursors of serotonin and dopamine at the aromatic amino acid decarboxylase.<sup>24,25,26</sup> Through its special formulation, R&R addresses the ability of serotonin concentrations increasing to induce or exacerbate hypoglutathionemia conditions (glutathione-related relative nutritional deficiency) secondary to conjugation between glutathione with 5-HTP, L-dopa, serotonin, and dopamine.<sup>27,28,29,30,31,32</sup>

### HOW SUPPLIED

R&R supplied in bottles of 180 pills (a one month supply).

### STORAGE

R&R should be stored at room temperature, avoid storage in temperatures above 100 degrees Fahrenheit.

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<sup>20</sup> Hyland, K. Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids, *J. Nutr.* 137: 1568S–1572S, 2007.

<sup>21</sup> Federal Register, Vol. 84, No. 130, Monday, July 8, 2019, Rules and Regulations, page 32,268

<sup>22</sup> Derek, M. et. al. Serotonin paracrine signaling in tissue fibrosis *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* Volume 1832, Issue 7, July 2013, Pages 905-910

<sup>23</sup> Cattaneo, M. et. al. Nicotine Stimulates a Serotonergic Autocrine Loop in Human Small-Cell Lung Carcinoma, *Cancer research* 53, November 15, 1993, 5566-5568

<sup>24</sup> KEGG Tryptophan metabolism pathway, [https://www.genome.jp/kegg-bin/show\\_pathway?org\\_name=hsa&mapno=00380&scale=&orgs=&auto\\_image=&nocolor=&show\\_description=hide](https://www.genome.jp/kegg-bin/show_pathway?org_name=hsa&mapno=00380&scale=&orgs=&auto_image=&nocolor=&show_description=hide) Accessed April 29, 2020

<sup>25</sup> KEGG Enzyme 4.12.1.28 [https://www.genome.jp/dbget-bin/www\\_bget?ec:4.1.1.28](https://www.genome.jp/dbget-bin/www_bget?ec:4.1.1.28) Accessed April 29, 2020

<sup>26</sup> Competitive inhibition definition <https://www.chem.wisc.edu/deptfiles/genchem/netorial/modules/biomolecules/modules/enzymes/enzyme5.htm> University of Wisconsin Department of Chemistry website, Last accessed October 25, 2019

<sup>27</sup> Oxford Dictionary, the definition of conjugation. [https://books.google.com/books?id=anecAQAAQBAJ&pg=PA369&lpg=PA369&dq=%22toxic+compounds+eliminated+from+the+body+by+conjugation+with+glutathione%22&source=bl&ots=T\\_kB8xpHEP&sig=ACfU3U21d3ExNWrBLxGKmMQLGR\\_OBkSotFg&hl=en&sa=X&ved=2ahUKewievKTFso7pAhXWWc0KHZ7PDh8Q6AEwAXoECA0QAO#v=onepage&q=%22toxic%20compounds%20eliminated%20from%20the%20body%20by%20conjugation%20with%20glutathione%22&f=false](https://books.google.com/books?id=anecAQAAQBAJ&pg=PA369&lpg=PA369&dq=%22toxic+compounds+eliminated+from+the+body+by+conjugation+with+glutathione%22&source=bl&ots=T_kB8xpHEP&sig=ACfU3U21d3ExNWrBLxGKmMQLGR_OBkSotFg&hl=en&sa=X&ved=2ahUKewievKTFso7pAhXWWc0KHZ7PDh8Q6AEwAXoECA0QAO#v=onepage&q=%22toxic%20compounds%20eliminated%20from%20the%20body%20by%20conjugation%20with%20glutathione%22&f=false) Accessed April 29, 2020

<sup>28</sup> Ballatori, N. et. al. Glutathione dysregulation and the etiology and progression of human diseases, *Biol Chem.* 2009 March; 390(3): 191–214

<sup>29</sup> Lu, S. Regulation of glutathione synthesis, *Mol Aspects Med.* 2009; 30(1-2): 42–59.

<sup>30</sup> Johnson, C. et. al. Vitamin C Elevates Red Blood Cell Glutathione in Healthy Adults, *Am J Clin Nutr.* 1993 Jul;58(1):103-5.

<sup>31</sup> Waly, M. et. al. Low Nourishment of Vitamin C Induces Glutathione Depletion and Oxidative Stress in Healthy Young Adults, *Prev. Nutr. Food Sci.* 2015;20(3):198-203

<sup>32</sup> Selenium-glutathione peroxidase EC 1.11.1.9, [https://www.genome.jp/dbget-bin/www\\_bget?ec:1.11.1.9](https://www.genome.jp/dbget-bin/www_bget?ec:1.11.1.9) Accessed April 29, 2020



**Description:**

Hyposerotonergic conditions or states occur when systemic serotonin concentrations on an optimized diet are not enough, low, inadequate, depleted, deficient, deficit, or suboptimal with a normal diet in place. Administration of nutrients required for optimal management of a hyposerotonergic condition is within a daily dosing range based on a medical evaluation group's findings, referred to as group one, or administered as a static daily (one size fits all), herein referred to as group two.

**R&R:**

R&R is the starting point in the management of a hyposerotonergic condition. R&R Sans is intended to be prescribed one week after starting R&R as needed and can be increased after one week if symptoms relating to a hyposerotonergic condition persists. See Table 1 for recommended dosing.

The categorization of the R&R nutrients is into one of two groupings. R&R and R&R Sans contain group one nutrients composed of the aromatic amino acid precursors of the centrally acting monoamines [L-tyrosine, Mucuna Pruriens (contains L-dopa), and 5-hydroxytryptophan (5-HTP)] which require daily dosing in a range defined by medical evaluation. All patients receiving group two nutrients receive the same daily dosing value (one size fits all). Group two nutrients include L-cysteine hydrochloride, vitamin C (ascorbic acid), calcium (as calcium citrate), vitamin B6 (as pyridoxal-5-phosphate), selenium (as selenium chelate), folate (as folic acid), and the starting dose of group one nutrients. R&R Sans contains group two nutrients required for optimal management of a hyposerotonergic condition and prevention of hypodopaminergic conditions or glutathionemia conditions by serotonin-related nutrients.

R&R contains the daily dosing requirement of group two nutrients, plus is the starting point for group one aromatic amino acid daily dosing. As determined by medical evaluation, the initial daily dosing value to R&R may achieve optimal results with some patients.

R&R's unique formulation provides necessary 5-HTP and vitamin B6 while being formulated to address the undesirable ability of aromatic amino acid precursors to induced hypodopaminergic or glutathionemia conditions or states.

**R&R Sans:**

Due to the static and variable dosing range of the nutrients required for optimal hyposerotonergic condition management, R&R Sans may need to be administered and can be administered concomitantly with R&R. Administration of enteral R&R Sans occurs under the supervision of a physician or other licensed caregiver for the dietary management of hyposerotonergic conditions or states for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. The hyposerotonergic condition or state has an increased requirement for serotonin precursor 5-HTP (in a variable dosing range) or vitamin B6 (as static daily dosing) to prevent serotonin-related symptoms or functional dysregulation when modification of the normal diet cannot manage these unique nutritional requirements.

A feature of R&R Sans not available with R&R is the ability to prescribe the aromatic amino acid precursors within a daily dosing range independent of the static daily dosing of group two



nutrients. For example, a patient whose feeding tube administration of nutrients contains adequate amounts of group two nutrients, based on medical evaluation, is administered R&R Sans group one aromatic amino acid nutrients within a dosing range for optimal hyposerotonergic condition management. Another example, the patient is started on R&R, then based on medical evaluation, there is a need to increase the daily dosing of 5-HTP. Increasing the daily dosing values of R&R, instead of administering R&R Sans, for the effect of increased 5-HTP may lead to excess administration of group two static daily dosed nutrients found in R&R.

R&R provides adequate daily dosing of group two nutrients. R&R Sans does not contain the group two nutrients, which requires static daily dosing. R&R Sans has group one composed of the aromatic amino acid precursors of the centrally acting monoamines found in R&R as the starting dose [L-tyrosine, Mucuna Pruriens (contains L-dopa), and 5-hydroxytryptophan (5-HTP)]. In group one, optimized patient results require individualized dosing within a daily dosing range. After the initial daily dosing of R&R for one week (see Table 1), R&R Sans is administered when a licensed health caregiver determines an increased daily dosing need of group one nutrients with no further increase in group two nutrients required.

**Intended Use:**

R&R Sans is a medical food formulated to be consumed or administered enterally under a healthcare professional's supervision and is intended for the specific dietary management of hyposerotonergic conditions or states. R&R Sans can be used in conjunction with R&R. Start R&R Sans one week after starting R&R when medical evaluation reveals hyposerotonergic condition is still present, see table 1.

Examples of hyposerotonergic condition etiologies while on a normal diet which may require R&R and R&R Sans based on medical evaluation, include but are not limited to: drug-induced serotonin depletion<sup>1,2,3,4,5</sup>, competitive inhibition serotonin depletion at the aromatic amino acid enzyme<sup>6,7</sup>, aromatic amino acid decarboxylase deficiency<sup>8</sup>, tetrahydrobiopterin (BH4) Deficiency<sup>9</sup>, genetic polymorphism G-T and G/A involving introne 6<sup>10</sup>, genetic serotonin transporter variance<sup>11</sup>, suboptimal serotonin concentrations, age-related serotonin suboptimal

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<sup>1</sup> Renoux C. et al. Association of Selective Serotonin Reuptake Inhibitors With the Risk for Spontaneous Intracranial Hemorrhage *AMA Neurol.* 2017;74(2):173-180.

<sup>2</sup> Schultz J. et al. Serotonergic agents increase the incidence of gastrointestinal bleeds in patients with continuous-flow left ventricular assist devices. *International Society for Heart Transplantation*, 05 Jan 2016, 35(6):823-824.

<sup>3</sup> Wagner A. et al. Effects of fluoxetine treatment of platelet 3H-imipramine binding, 5-HT uptake and 5-HT content in major depressive disorder *Journal of Affective Disorders* Volume 20, Issue 2, October 1990, Pages 101-113.

<sup>4</sup> Maurer-Spurej E. et al. The influence of selective serotonin reuptake inhibitors on human platelet serotonin *Thromb Haemost* 2004; 91: 119-28.

<sup>5</sup> Gagne, J. et al. Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting: A Cohort Study *Drug Safety* volume 38, pages1075–1082 (2015).

<sup>6</sup> Stansley, B., Yamamoto B. L-Dopa and Brain Serotonin System Dysfunction *Toxics* 2015, 3, 75-88.

<sup>7</sup> Garcia N. et al. Chronic oral L-DOPA increases dopamine and decreases serotonin excretions *Am J Physiol Regulatory Integrative Comp Physiol* 277:1476-1480, 1999.

<sup>8</sup> Hyland K., Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids *Journal of Nutrition*, Volume 137, Issue 6, June 2007, Pages 1568S–1572S.

<sup>9</sup> Federal Register Vol. 84, No. 130 July 8, 2019 p. 32268.

<sup>10</sup> I. Paclt1, J. Koudelová, A. Křepelová, P. Uhlíková, M. Gazdíková & P. Bauer Biochemical markers and genetic research of ADHD *Neuroendocrinol Lett* 2005; 26(4):423–430.

<sup>11</sup> Offenbaecher M. et al. Possible association of fibromyalgia with a polymorphism in the serotonin receptor gene regulatory region, *Arthritis & Rheumatism* Vol. 42, No. 11, November 1999, pp 2482–2488.



serotonin concentrations<sup>12</sup>, decreased serotonin transporter activity<sup>13</sup>, increased numbers (and activity) of SERT (serotonin transporters) or a loss of serotonergic neurons<sup>14</sup>, low serotonin associated with Parkinson's disease<sup>15</sup>, low serotonin associated with Post-traumatic stress disorder<sup>16</sup>, low serotonin associated with chronic tension headache and migraine<sup>17</sup>, low serotonin related to fibromyalgia<sup>18</sup>, and neurotoxin-induced hyposerotonergic condition.<sup>19</sup>

**Dosage, Administration, Ingredients:**

**NOTICE: THIS PRODUCT IS INTENDED FOR USE ONLY UNDER THE DIRECT SUPERVISION OF A PHYSICIAN OR OTHER LICENSED HEALTHCARE PRACTITIONER.**

**Dosing**

Take as directed by your caregiver. R&R Sans is intended for concomitant administration with R&R. Table 1 illustrates a recommended dosing schedule. Nutrients requiring static daily dosing (not a dosing range) are only in R&R. Increasing the daily dose of R&R above six tablets per day may give rise to hypervitaminosis concerns.

		<b>Morning</b>	<b>Noon</b>	<b>Evening</b>
<b>First Visit</b>	<b>Level One</b>	2 pills R&R	2 pills R&R	2 pills R&R
<b>In 7 days, if still with symptoms</b>	<b>Level Two</b>	2 pills R&R	2 pills R&R 1 pill R&R Sans	2 pills R&R 1 pill R&R Sans
<b>In 7 days, if still with symptoms</b>	<b>Level Three</b>	2 pills R&R	2 pills R&R 2 pills R&R Sans	2 pills R&R 2 pills R&R Sans

Table 1: The initial daily dosing of R&R along with addition of R&R Sans in seven and fourteen days of optimal relief of hyposerotonergic condition-related symptoms is not achieved.

<sup>12</sup> Nitkita L. et al. The impact of protein supplementation on cognitive performance in frail elderly Eur J Nutr 2014 Apr;53(3):803-12.

<sup>13</sup> Shih-Hsien L. et al. Serotonin and Mental Disorders: A Concise Review on Molecular Neuroimaging Evidence Clinical Psychopharmacology and Neuroscience 2014;12(3):196-202.

<sup>14</sup> Hess S. et al. Advances in vivo imaging of serotonergic neurons in neuropsychiatric disorders Neuroscience and Biobehavioral Reviews 28 (2004) 547–563.

<sup>15</sup> Tan S. et al. Serotonin-dependent depression in Parkinson’s disease: A role for the subthalamic nucleus Neuropharmacology 61 (2011) 387e399.

<sup>16</sup> DeBellis M. et al. Biologic Findings of Post-traumatic Stress Disorder and Child Maltreatment Current Psychiatry Reports 2003, 5:108–117.

<sup>17</sup> Anthony, M. Plasma serotonin in patients with chronic tension headaches Journal of Neurology, Neurosurgery, and Psychiatry 1989;52:182-184.

<sup>18</sup> Amin O. et al. Clinical association of vitamin D and serotonin levels among patients with fibromyalgia syndrome Neuropsychiatric Disease and Treatment 2019;15 1421–1426.

<sup>19</sup> McCann U. et al. Positron emission tomographic evidence of toxic effect of MDMA (“Ecstasy”) on brain serotonin neurons in human beings Lancet 1998; 352: 1433–37.



**Ingredients**

R&R Sans is a white 1.59 cm non-scored round white 600 milligram pill. Active ingredients include:

- L-tyrosine
- Mucuna Pruriens (active ingredient 40% L-dopa)
- 5-hydroxytryptophan

**Discontinuation**

There are no known adverse events or reactions associated with the abrupt stopping of R&R or R&R Sans.

**Contraindications, Warning and Precautions:**

**Contraindications**

Administering R&R Sans to patients with known hypersensitivity to the product components is contraindicated.

**Pregnancy**

No studies demonstrate the active ingredients in R&R Sans cause pregnancy problems or are safe.

**Renal or hepatic impairment**

There has been no documented elevation of renal or hepatic enzymes attributed to the nutrients found in R&R or R&R Sans.

**Adverse reactions**

Side effects may include dry mouth, insomnia, headache, nausea, dizziness, and constipation.

**Drug Interactions**

The medical food R&R Sans can increase systemic serotonin concentrations beyond the ability of the normal diet. As can occur at any point during drug administration, a side effect may occur.

**Overdose**

Overdose symptoms may include diarrhea, weakness, and nausea. Should poisoning concerns arise, contact the local poison control.

**Clinical Pharmacology:**

Relative nutritional deficiency occurs when a normal diet does not meet the needs of the system. When systemic serotonin concentrations are not enough, low, inadequate, depleted, deficient, or suboptimal on a normal diet, the hyposerotonergic condition or state is caused by a serotonin-related relative nutritional deficiency exists.

On a normal diet, L-tryptophan is the primary amino acid precursor metabolized to serotonin. A limitation of the amount of serotonin synthesized is regulated by the enzyme tryptophan hydroxylase, which restricts (limits) the metabolism of L-tryptophan to 5-hydroxytryptophan (5-HTP). When adequate cofactor (vitamin B6) activated enzyme concentrations exist, the only



substance which can increase serotonin concentrations higher than can be achieved with L-tryptophan from the optimized normal diet is 5-HTP, the immediate amino acid precursor of serotonin.<sup>20,21,22,23</sup>

The concomitant administration of R&R and R&R Sans medical foods addresses the ability of 5-HTP to induce or exacerbate hypodopaminergic conditions.<sup>24,25,26</sup> Through its special formulation, R&R is required with R&R Sans to address the ability of increasing concentrations of serotonin, dopamine, and precursors to cause or exacerbate hypoglutathionemia conditions (glutathione-related relative nutritional deficiency) secondary to conjugation between glutathione with 5-HTP, L-dopa, serotonin, and dopamine.<sup>27,28,29,30,31,32</sup>

### HOW SUPPLIED

R&R Sans is in bottles of 60 pills (a one-month supply).

### STORAGE

Store R&R Sans at room temperature; avoid storage in temperatures above 100 degrees Fahrenheit.

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<sup>20</sup> Hyland, K. Inherited Disorders Affecting Dopamine and Serotonin: Critical Neurotransmitters Derived from Aromatic Amino Acids, *J. Nutr.* 137: 1568S–1572S, 2007.

<sup>21</sup> Federal Register, Vol. 84, No. 130, Monday, July 8, 2019, Rules and Regulations, page 32,268.

<sup>22</sup> Derek, M. et. al. Serotonin paracrine signaling in tissue fibrosis *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* Volume 1832, Issue 7, July 2013, Pages 905-910.

<sup>23</sup> Cattaneo, M. et. al. Nicotine Stimulates a Serotonergic Autocrine Loop in Human Small-Cell Lung Carcinoma, *Cancer research* 53, November 15, 1993, 5566-5568.

<sup>24</sup> KEGG Tryptophan metabolism pathway, [https://www.genome.jp/kegg-bin/show\\_pathway?org\\_name=hsa&mapno=00380&scale=&orgs=&auto\\_image=&nocolor=&show\\_description=hide](https://www.genome.jp/kegg-bin/show_pathway?org_name=hsa&mapno=00380&scale=&orgs=&auto_image=&nocolor=&show_description=hide) Accessed April 29, 2020.

<sup>25</sup> KEGG Enzyme 4.12.1.28 [https://www.genome.jp/dbget-bin/www\\_bget?ec:4.1.1.28](https://www.genome.jp/dbget-bin/www_bget?ec:4.1.1.28) Accessed April 29, 2020.

<sup>26</sup> Competitive inhibition definition <https://www.chem.wisc.edu/deptfiles/genchem/netorial/modules/biomolecules/modules/enzymes/enzyme5.htm> University of Wisconsin Department of Chemistry website, Last accessed October 25, 2019.

<sup>27</sup> Oxford Dictionary, the definition of conjugation.

[https://books.google.com/books?id=anecAQAAQBAJ&pg=PA369&lpg=PA369&dq=%22toxic+compounds+eliminated+from+the+body+by+conjugation+with+glutathione%22&source=bl&ots=T\\_kB8xpHEP&sig=ACfU3U21d3ExNWrlxGKmMQLGR\\_OBkSotFg&hl=en&sa=X&ved=2ahUKewievKTFso7pAhXWWc0KHZ7PDh8Q6AEwAXoECA0QAQ#v=onepage&q=%22toxic%20compounds%20eliminated%20from%20the%20body%20by%20conjugation%20with%20glutathione%22&f=false](https://books.google.com/books?id=anecAQAAQBAJ&pg=PA369&lpg=PA369&dq=%22toxic+compounds+eliminated+from+the+body+by+conjugation+with+glutathione%22&source=bl&ots=T_kB8xpHEP&sig=ACfU3U21d3ExNWrlxGKmMQLGR_OBkSotFg&hl=en&sa=X&ved=2ahUKewievKTFso7pAhXWWc0KHZ7PDh8Q6AEwAXoECA0QAQ#v=onepage&q=%22toxic%20compounds%20eliminated%20from%20the%20body%20by%20conjugation%20with%20glutathione%22&f=false) Accessed April 29, 2020.

<sup>28</sup> Ballatori, N. et. al. Glutathione dysregulation and the etiology and progression of human diseases, *Biol Chem.* 2009 March; 390(3): 191–214.

<sup>29</sup> Lu, S. Regulation of glutathione synthesis, *Mol Aspects Med.* 2009; 30(1-2): 42–59.

<sup>30</sup> Johnson, C. et. al. Vitamin C Elevates Red Blood Cell Glutathione in Healthy Adults, *Am J Clin Nutr.* 1993 Jul;58(1):103-5.

<sup>31</sup> Waly, M. et. al. Low Nourishment of Vitamin C Induces Glutathione Depletion and Oxidative Stress in Healthy Young Adults, *Prev. Nutr. Food Sci.* 2015;20(3):198-203.

<sup>32</sup> Selenium-glutathione peroxidase EC 1.11.1.9, [https://www.genome.jp/dbget-bin/www\\_bget?ec:1.11.1.9](https://www.genome.jp/dbget-bin/www_bget?ec:1.11.1.9) Accessed April 29, 2020.