



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

R&R Sans™ Product Insert

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^{1,2,3,4,5}, competitive inhibition serotonin depletion at the aromatic amino acid enzyme^{6,7}, aromatic amino acid decarboxylase deficiency⁸, tetrahydrobiopterin (BH4) Deficiency⁹, genetic polymorphism G-T and G/A involving introne 6¹⁰, genetic serotonin transporter variance¹¹, suboptimal serotonin concentrations, age-related serotonin suboptimal

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

² 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.

³ 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.

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

⁵ 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).

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

⁷ 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.

⁸ 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.

⁹ Federal Register Vol. 84, No. 130 July 8, 2019 p. 32268.

¹⁰ 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.

¹¹ 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 Sans™ Product Insert

serotonin concentrations¹², decreased serotonin transporter activity¹³, increased numbers (and activity) of SERT (serotonin transporters) or a loss of serotonergic neurons¹⁴, low serotonin associated with Parkinson's disease¹⁵, low serotonin associated with Post-traumatic stress disorder¹⁶, low serotonin associated with chronic tension headache and migraine¹⁷, low serotonin related to fibromyalgia¹⁸, and neurotoxin-induced hyposerotonergic condition.¹⁹

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.

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

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

¹³ 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.

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

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

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

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

¹⁸ 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.

¹⁹ 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.

R&R Sans™ Product Insert

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

R&R Sans™ Product Insert

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.^{20,21,22,23}

The concomitant administration of R&R and R&R Sans medical foods addresses the ability of 5-HTP to induce or exacerbate hypodopaminergic conditions.^{24,25,26} 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.^{27,28,29,30,31,32}

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.

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

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

²² 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.

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

²⁴ 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 Accessed April 29, 2020.

²⁵ KEGG Enzyme 4.12.1.28 https://www.genome.jp/dbget-bin/www_bget?ec:4.1.1.28 Accessed April 29, 2020.

²⁶ 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.

²⁷ 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 Accessed April 29, 2020.

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

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

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

³¹ 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.

³² Selenium-glutathione peroxidase EC 1.11.1.9, https://www.genome.jp/dbget-bin/www_bget?ec:1.11.1.9 Accessed April 29, 2020.