NOVADOZ
AN MSN COMPANY

SIROLIMUS ORAL SOLUTION 1mg/mL

S.No.	Category	Question	Answer
Clinical Particulars			
1	Use/Indication	What is the product indicated for?	Sirolimus oral solution is an mTOR inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants: • Patients at low- to moderate-immunologic risk: Use initially with cyclosporine (CsA) and corticosteroids. CsA withdrawal is recommended 2-4 months after transplantation. • Patients at high-immunologic risk: Use in combination with CsA and corticosteroids for the first 12 months following transplantation. Safety and efficacy of CsA withdrawal has not been established in high risk patients. • Sirolimus oral solution is an mTOR inhibitor indicated for the treatment of patients with lymphangioleiomyomatosis.
2	Dosage	What is the recommended dosage?	The recommended dosage of Sirolimus oral solution is: Dose: 60 mg per 60 mL in amber glass bottle. **In renal transplant patients at low-to moderate-immunologic risk:** • Sirolimus oral solution and CsA Combination Therapy: One loading dose of 6 mg on day 1, followed by daily maintenance doses of 2 mg. • Sirolimus oral solution Following CsA Withdrawal: 2-4 months post-transplantation, withdraw CsA over 4-8 weeks. **In renal transplant patients at high-immunologic risk*:*** • Sirolimus oral solution and CsA Combination Therapy (for the first 12 months post-transplantation): One loading dose of up to 15 mg on day 1, followed by daily maintenance doses of 5 mg. **<u>Lymphangioleiomyomatosis Patients:</u>** • Administer once daily by mouth, consistently with or without food. • Recommended initial sirolimus oral solution dose

			is 2 mg/day. • Adjust the sirolimus oral solution dose to achieve sirolimus trough concentrations between 5-15 ng/mL. • Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment
3	Administration	How do I take it?	Sirolimus oral solution is to be administered orally once daily, consistently with or without food
4	Formulation	Can tablet be crushed?	NO
5	Administration	What do I do if I miss a dose?	If you miss a dose of Sirolimus oral solution continue your prescribed course of therapy, and contact your physician immediately.
6	Administration	Use in Pediatric Population	The safety and efficacy of sirolimus in pediatric patients under 13 years have not been established. However, sirolimus oral solution and tablets have been proven effective for prophylaxis of organ rejection in children aged 13 years and older with low- to moderate-immunologic risk. This use is supported by trials in adults and pharmacokinetic data in pediatric patients. In pediatric and adolescent patients at high-immunologic risk (history of acute rejection episodes or chronic allograft nephropathy), chronic use of sirolimus in combination with calcineurin inhibitors and corticosteroids is not recommended. This combination is associated with a higher incidence of lipid abnormalities and renal function deterioration, without added benefits in acute rejection or graft survival. **Lymphangioleiomyomatosis** The safety and efficacy of sirolimus in pediatric patients under 18 years have not been established..
7	Administration	Use in Geriatric Population	Clinical studies of sirolimus oral solution or Tablets did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary. Differences in responses between the elderly and younger patients have not been identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, or cardiac function, and of concomitant disease or other drug therapy.

8	Mechanism	Mechanism of Action	Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus: FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1to the S phase of the cell cycle. Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been shown in vitro to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. In lymphangioleiomyomatosis, characterized by lung tissue infiltration by LAM cells (which have inactivating mutations of the tuberous sclerosis complex gene), sirolimus inhibits the activated mTOR pathway, thereby reducing LAM cell proliferation.
9	Warning	Black Box Warning	• WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS • **Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression** • **Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use sirolimus for prophylaxis of organ rejection in patients receiving renal transplants. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.** • **The safety and efficacy of sirolimus as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.** • **Liver Transplantation –**

			Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT • **The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in *de novo* liver transplant patients. Many of these patients had evidence of infection at or near the time of death.** • **In this and another study in *de novo* liver transplant patients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death** • **Lung Transplantation – Bronchial Anastomotic Dehiscence** • **Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.**
10	Lactation	Use in Lactation	It is not known whether sirolimus is present in human milk. There are no data on its effects on the breastfed infant or milk production. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Sirolimus is present in the milk of lactating rats. There is potential for serious adverse effects from sirolimus in breastfed infants based on mechanism of action. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sirolimus and any potential adverse effects on the breastfed child from sirolimus.
11	Pregnancy	Use in Pregnancy	Based on animal studies and the mechanism of action, sirolimus can cause foetal harm when administered to a pregnant woman. There are limited data on the use of sirolimus during pregnancy; however, these data are insufficient to inform a drug-associated risk of adverse developmental outcomes. In animal studies, sirolimus was embryo/fetotoxic in rats at sub-therapeutic doses. Advise pregnant women of the potential risk to a foetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

12	Precautions	Is there any interaction between medication and alcohol?	None
13	Interaction	Is there any interaction with food?	Take each dose of sirolimus oral solution the same way, either with or without food. Food can affect the amount of medicine that gets into your bloodstream. **Grapefruit Juice** Grapefruit juice inhibits CYP3A4-mediated drug metabolism, which can significantly affect sirolimus levels. It should not be consumed or used to dilute sirolimus. **St. John's Wort** St. John's Wort induces CYP3A4 and P-glycoprotein (P-gp). As sirolimus is a substrate for both, using St. John's Wort in patients taking sirolimus may lead to reduced sirolimus concentrations.
14	Side effects	What are the common side effects?	Serious Side Effects of Sirolimus Oral Solution **Allergic Reactions** Seek immediate medical help if you experience: • Swelling of the face, eyes, or mouth • Chest pain or tightness • Trouble breathing or wheezing • Dizziness or fainting • Throat tightness • Rash or skin peeling **Edema** Fluid retention may occur, leading to swelling in the hands, feet, or around the heart and lungs. Contact your doctor if you have trouble breathing. **Poor Wound Healing** Sirolimus can slow wound healing. Inform your doctor of any redness, drainage, or if a wound does not heal properly. **Increased Lipids** Blood tests should monitor cholesterol and triglyceride levels, which may remain high despite treatment. **Kidney Function** Sirolimus can affect kidney function, especially when taken with cyclosporine. Regular kidney function tests are recommended. **Protein in Urine**

			Your doctor may monitor urine for protein levels. **Increased Infection Risk** Be aware of potential viral infections, including BK virus and Progressive Multifocal Leukoencephalopathy (PML). Seek medical attention for symptoms like confusion or sudden weakness. **Lung Issues** Notify your doctor of any new or worsening respiratory symptoms. **Blood Clotting Problems** Unexplained bleeding or bruising should be reported to your doctor, especially if taking with cyclosporine or tacrolimus. **Pregnancy Risks** Sirolimus can harm an unborn baby. Avoid pregnancy during treatment and for 12 weeks afterward. **Common Side Effects** **In Renal Transplant Patients:** • High blood pressure • Urinary tract infections • Pain (stomach and joint) • Anemia • Diarrhea • Nausea • Headache • Low platelet count • Fever • High blood sugar **In LAM Patients:** • Mouth sores • Chest pain • Diarrhea • Upper respiratory infections • Stomach pain • Headache • Nausea • Dizziness • Sore throat • Muscle pain

			• Acne **Other Considerations** Sirolimus may affect fertility in both males and females. Consult your healthcare provider if this is a concern. Report any bothersome or persistent side effects to your doctor. This is not a comprehensive list of side effects; for more information, consult your healthcare provider or pharmacist.
15	Storage	What are the storage conditions?	• Store bottles of sirolimus oral solution in the refrigerator between 36°F to 46°F (2°C to 8°C). • Protect from light. • If necessary, bottles of sirolimus oral solution can be stored at room temperature up to 77°F (25°C) for up to 15 days. • When a bottle of sirolimus oral solution is opened, it should be used within 1 month. • Use any diluted sirolimus oral solution right away.
16	Dispensing	How to Dispense?	As prescribed by the Physician
17	Contraindication	What are the contraindications of (medication).	Sirolimus is contraindicated in patients with a hypersensitivity to sirolimus
Pharmaceutical Particulars			
18	Pharmaceutical Form	How is it supplied?	sirolimus oral solution is not absorbed through the skin, there are no special precautions. However, if direct contact of the oral solution occurs with the skin or eyes, wash skin thoroughly with soap and water; rinse eyes with plain water. Do not use sirolimus oral solution after the expiration date. The expiration date refers to the last day of that month.
19	Ingredients	Active and Inactive Ingredients	**Active** sirolimus **Inactive**: Phosal 50 PG® (phosphatidylcholine, propylene glycol, sunflower seed oil glyceride, ethanol, soy fatty acids, ascorbyl palmitate and tocopherol) and polysorbate 80. sirolimus oral solution contains 1.5%- 2.5% ethanol.
20	Coating	What is the type of coating?	None
Allergens			
21	Ingredients	Is it Vegetarian?	yes

22	Ingredients	Does it contain Gluten?	No
23	Ingredients	Does it contain Dairy Products?	No
24	Ingredients	Does it contain Casein	No
25	Ingredients	Does it contain Whey?	No
26	Ingredients	Does it contain corn?	No
27	Ingredients	Does it contain rye?	No
28	Ingredients	Does it contain sugar?	No
29	Ingredients	Does it contain Oats?	No
30	Ingredients	Does it contain wheat?	No
31	Ingredients	Does it contain spelt?	No
32	Ingredients	Does it contain barley?	No
33	Ingredients	Does it contain rennet?	No
34	Ingredients	Does it contain starch?	No
35	Ingredients	Does it contain Iodine?	No
36	Ingredients	Does it contain latex?	No
37	Ingredients	Does it contain alcohol?	Yes
38	Ingredients	Does it contain dyes?	No
39	Ingredients	Does it contain flavor?	No
40	Ingredients	Does it contain Lactose?	No
41	Ingredients	Does it contain Nuts?	No
42	Ingredients	Does it contain Preservatives?	No
43	Ingredients	Does it contain Soy products?	No
44	Ingredients	Does it contain peanut?	No
45	Ingredients	Does it contain nickel?	No
46			
Miscellaneous	Miscellaneous	May I know the product availability?	Novadoz Pharmaceuticals products are only available through pharmacies, wholesalers, and other authorized distributors. See our ADR (authorized distributors of record) page at NovadozPharma.com to learn more about

			where to find our products.
47	Miscellaneous	May I know about return, refunds and reimbursement?	Contact Novadoz Pharmaceuticals Customer Service directly at 908-360-1500
48	Miscellaneous	Do you have any patient's assistance program?	Novadoz Pharmaceuticals does not offer patient assistance programs at this time. The company that produces the brand version of your product may or may not offer such a program. Please check for access & eligibility requirements with that company.
49	Miscellaneous	How do I report an adverse drug effect or reaction to Novadoz medication?	To report suspected adverse reactions, contact Novadoz Pharmaceuticals LLC at 1-855-668-2369 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
50	Miscellaneous	Why does my pharmacy that used to fill your generic formulation of a particular medicine, no longer fills my prescription with Novadoz formulation?	Please check with your pharmacy as to why your prescription is not a Novadoz Pharmaceuticals product. You may refer to NovadozPharma.com ADR (authorized distributor of record) page to learn where to find our products.
51	Miscellaneous	Manufacturer and Distributor	**Manufactured by:** **MSN Pharmaceuticals Inc.** **Piscataway, NJ 08854** **Distributed by:** **Novadoz Pharmaceuticals LLC** **Piscataway, NJ 08854 -3714**