Cabergoline is a dopamine receptor agonist that has been used as a medical therapy in the management of Cushing's disease, particularly in patients who are not candidates for surgery or have persistent or recurrent disease after surgery. While it is more commonly used in the treatment of prolactinomas, its role in Cushing's disease has been explored due to its ability to reduce ACTH production in some pituitary adenomas.

1. Indications for Cabergoline in Cushing's Disease: Persistent or recurrent disease: After transsphenoidal surgery, patients who continue to have elevated cortisol levels may benefit from cabergoline as an adjunct therapy. Surgery not feasible: In patients who are poor surgical candidates due to medical comorbidities or who refuse surgery. Mild to moderate hypercortisolism: Cabergoline is generally more effective in patients with lower levels of cortisol elevation compared to those with severe hypercortisolism. Combination therapy: In some cases, cabergoline may be used in combination with other medications, such as ketoconazole or pasireotide, to enhance the overall effectiveness of medical treatment for Cushing's disease. 2. Mechanism of Action: Cabergoline acts as a dopamine D2 receptor agonist. Some ACTH-secreting pituitary adenomas express dopamine receptors, and cabergoline can reduce ACTH secretion by stimulating these receptors. By decreasing ACTH production, cabergoline can lower cortisol levels, alleviating the symptoms of hypercortisolism. 3. Effectiveness: Variable response: Studies show that cabergoline is effective in 30-40% of patients with Cushing's disease, with some achieving normal cortisol levels (biochemical remission). Higher doses: Higher doses of cabergoline (up to 3.5 mg per week) may be required for patients with Cushing's disease, compared to the lower doses typically used for prolactinomas. Long-term control: In some cases, cabergoline has been shown to provide long-term control of cortisol levels, though its efficacy can decrease over time due to tachyphylaxis (a reduction in response to the medication). 4. Advantages: Oral administration: Cabergoline is administered orally, making it a convenient option for long-term management. Well-tolerated: Most patients tolerate cabergoline well, with relatively few side effects. Dual action: In cases where patients have both prolactinomas and Cushing's disease, cabergoline can simultaneously manage both conditions. 5. Side Effects: Nausea, vomiting, dizziness, and headache are the most common side effects. Valvular heart disease: There is concern about the risk of cardiac valve fibrosis with high doses of dopamine agonists like cabergoline, especially in patients taking long-term therapy at higher doses. Routine monitoring with echocardiograms may be recommended. Psychiatric effects: Some patients may experience mood changes, depression, or impulse control disorders (e.g., gambling, hypersexuality). 6. Limitations: Not effective in all patients: Cabergoline's efficacy is limited to a subset of patients with Cushing's disease. Those with large macroadenomas or tumors without dopamine receptor expression are less likely to respond. Loss of efficacy: Over time, some patients may experience a reduction in the drug's effectiveness, necessitating a change in therapy or an increase in dosage. Combination therapy often needed: In many cases, cabergoline alone may not be sufficient to control cortisol levels, and patients may need additional medications or radiation therapy. 7. Monitoring and Follow-up: Cortisol levels: Patients on cabergoline need regular monitoring of serum cortisol and 24-hour urinary free cortisol levels to assess the effectiveness of the therapy. MRI scans: Periodic imaging of the pituitary is required to assess tumor size and potential changes in adenoma volume. Cardiac monitoring: Due to the risk of valvulopathy, patients on long-term, high-dose cabergoline may need regular echocardiograms to monitor for valvular disease. 8. Comparison with Other Medical Therapies: Pasireotide: Another medical option for Cushing's disease that targets somatostatin receptors. Pasireotide may be more effective but comes with higher risks of hyperglycemia. Ketoconazole or metyrapone: These drugs directly inhibit cortisol synthesis but do not address the source of ACTH production, unlike cabergoline, which reduces ACTH production. Mifepristone: A cortisol receptor antagonist that can control the symptoms of hypercortisolism but does not reduce cortisol levels. 9. Role in Combination Therapy: Cabergoline can be used in combination with other medical therapies such as ketoconazole or mitotane, or even alongside stereotactic radiosurgery in patients who have residual or recurrent disease post-surgery. Summary: Cabergoline is a dopamine agonist that is used as a second-line

treatment for Cushing’s disease, particularly in patients with persistent or recurrent disease after surgery or those who are not surgical candidates. Its efficacy is variable, and it is most beneficial in patients with mild to moderate hypercortisolism. While generally well-tolerated, potential side effects such as valvulopathy and mood disturbances require careful monitoring.