Setmelanotide (IMCIVREE) — Basic Review Questions

1. What is setmelanotide, what type of peptide is it, and what is its regulatory status?

Answer: Setmelanotide (brand name IMCIVREE) is a selective MC4R (melanocortin-4 receptor) agonist — a small cyclic peptide given by once-daily subcutaneous injection. It is an FDA-approved obesity drug, but its approval is narrow: it is only for chronic weight management in people with specific, genetically confirmed defects in the body's satiety pathway (POMC, PCSK1, or LEPR deficiency, and Bardet-Biedl syndrome), age 6 and up. Genetic testing confirming the mutation is required before it can be used.

2. How does setmelanotide work?

Answer: It works on the leptin-melanocortin pathway — the brain circuit that signals the body has had enough to eat. Normally, leptin from fat tissue triggers a chain (leptin → POMC → alpha-MSH → MC4R) that produces a satiety signal and raises energy expenditure. In the patients it treats, a genetic mutation breaks one of the upstream steps, so no satiety signal is made and they experience relentless hunger (hyperphagia). Setmelanotide acts directly at the final receptor, MC4R, delivering the missing signal and bypassing whatever upstream step is broken — restoring satiety and increasing energy use.

3. Who is setmelanotide for, and why is genetic testing required first?

Answer: Because the drug only helps if the obesity is actually caused by a defect in that specific pathway. It works by supplying the missing MC4R signal — so if a person's satiety system is already intact (ordinary obesity), adding the signal does little while still exposing them to side effects. Genetic confirmation of a disease-causing variant in POMC, PCSK1, LEPR, or a Bardet-Biedl gene is therefore the gateway to treatment; it is explicitly not approved for general obesity.

4. How is setmelanotide different from the GLP-1 drugs and other obesity treatments?

Answer: The GLP-1-type drugs (semaglutide, tirzepatide, and so on) suppress an otherwise-working appetite system and are used broadly for common obesity. Setmelanotide does something fundamentally different: it corrects a specific broken signal in people whose satiety pathway is genetically disabled. So it is precision medicine for a small, defined population rather than a general weight-loss drug — and patients often describe the result not as reduced appetite but as having a normal appetite for the first time. (Mechanistically it is a melanocortin-receptor drug, in the same family as PT-141, rather than a gut-hormone/incretin drug.)

5. What are the results, and what happens if the drug is stopped?

Answer: The results in the right patients are striking: about 80% of those with POMC or PCSK1 deficiency lost at least 10% of body weight in a year (higher than typical general-obesity drugs), with a somewhat lower response in LEPR deficiency. Often the most meaningful change for patients and families is the dramatic reduction in compulsive hunger, which can appear within weeks, even before much weight is lost. Because the underlying genetic defect does not go away, weight is regained when the drug is stopped — so it is a long-term, ongoing treatment.

6. What are the main safety concerns with setmelanotide?

Answer: The most serious is a black box warning for depression and suicidal ideation, so formal psychiatric screening before starting and regular monitoring are required. Because it has minor off-target activity at the pigment receptor (MC1R), skin and mole darkening is very common (around 80%) — reversible after stopping, but it warrants skin checks. Injection-site reactions and early nausea are also common. Reassuringly, unlike older MC4R drugs, it does not raise heart rate or blood pressure. Finally, because MC4R activation is linked to sexual arousal (the same mechanism as PT-141), it can cause spontaneous erections in men, with a priapism caution if combined with erectile-dysfunction drugs.