**Suppl 4.** Summary of Findings: Adverse Reactions

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| **Drug** | **Trials (pop.)** | **Overall safety profile** | **Certainty (GRADE)** |
| Elagolix | 2 RCTs (≈ 1,500 pts) | Common hypoestrogenic AEs (hot flush ~30-70% vs. ~8-23% with placebo); headache/nausea also frequent. Dose-dependent BMD loss (lumbar spine ∼5-15%). TEAE discontinuations were low. | Moderate (see above) |
| Relugolix | 2 RCTs (≈ 800 pts with add-back) | Generally well tolerated; headaches and hot flushes common but less severe due to estrogen add-back. Minimal BMD loss (~0.7% decrease vs. +0.2% on placebo in 6 mo). Low discontinuation (no serious AEs). | Moderate (indirectness from add-back; imprecision) |
| Linzagolix | 1-2 studies (few hundred pts) | Good symptom relief with mostly mild AEs; headache (~15-20%) and hot flush (~10-12%) were most common. BMD decline modest at low doses (< 1%); higher doses cause more loss (∼2-3%). Few serious AEs or withdrawals. | Low (limited data) |
| ASP1707 | 1 RCT (532 pts) | Favorable safety: lower hypoestrogenic effects than GnRH agonists. Hot flushes (15%) and headache (14%) occurred but less than with leuprolide. BMD loss was dose-dependent but significantly less than GnRH agonist. Overall TEAEs ~57% (similar to placebo). | Low (single small trial) |