Menopause — NK Receptor Antagonists

Fezolinetant & elinzanetant — a new non-hormonal class

CLINICAL PATHWAY

Neurokinin (NK) receptor antagonists are a first-in-class, targeted non-hormonal option for VMS, acting on the hypothalamic KNDy pathway rather than serotonin/noradrenaline. Both require a private prescription in Australia and PBS status is changing — confirm current TGA/PBS status before prescribing.

MECHANISM — THE KNDy PATHWAY

Kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamus regulate the thermoregulatory centre — normally inhibited by estrogen, stimulated by neurokinin B. At menopause, falling estrogen leaves KNDy neurons unopposed and hyperactive, destabilising thermoregulation and causing hot flushes and night sweats. NK receptor antagonists block this signal directly, without using estrogen.

FEZOLINETANT (VEOZA)

- NK3 antagonist; TGA-approved 2024. 45mg orally once daily, no titration; effect usually within 1–2 weeks.
- SKYLIGHT trials: roughly 60–65% reduction in moderate-severe VMS frequency at 12 weeks, sustained to 52 weeks.
- Hepatotoxicity — TGA safety update (Oct 2025): check LFTs at baseline, monthly for the first 3 months, then at 6 and 9 months, then periodically.
- Avoid with strong CYP1A2 inhibitors (e.g. ciprofloxacin, fluvoxamine); smokers may need a higher dose (faster metabolism).

ELINZANETANT (LYNKUET)

- Dual NK1 + NK3 antagonist; TGA-registered 2025–26, Schedule 4. The NK1 component may add a sleep benefit.
- OASIS trials: roughly 74% reduction in moderate-severe VMS at 12 weeks, with improved sleep and menopause-specific quality of life.
- OASIS-4: positive result specifically in breast cancer patients on endocrine therapy — a relevant option for this group.
- Common adverse effects: headache, fatigue, dizziness, somnolence (mostly mild-moderate). No specific LFT monitoring schedule mandated, unlike fezolinetant.

AUSTRALIAN ACCESS

Both currently require a private prescription — as of mid-2026, neither is PBS-listed (fezolinetant's PBAC submission was not recommended at the March 2025 meeting). This is a fast-moving area; confirm current TGA registration and PBS status at tga.gov.au and pbs.gov.au before prescribing.

WHO MIGHT SUIT THIS CLASS

- Breast cancer survivors wanting a non-hormonal option, especially on endocrine therapy.
- Refractory VMS despite an adequate SSRI/SNRI or gabapentinoid trial (see companion sheet WH-06A).

■ SAFETY

- Fezolinetant: stop immediately and check LFTs if symptoms suggest hepatotoxicity (new fatigue, nausea, jaundice, dark urine, abdominal pain); follow the TGA's monthly-then-6/9-month monitoring schedule.
- Both agents are under additional TGA monitoring (Black Triangle Scheme) as newer medicines — report any suspected adverse effects.

■ RED FLAGS / REFER

- Inadequate response despite an adequate trial of an NK receptor antagonist.
- Abnormal LFTs on fezolinetant.
- Complex interaction with breast cancer endocrine therapy needing oncology input.

Companion sheets: WH-06A (SSRIs/SNRIs & established agents), WH-06C (GSM, lifestyle & complementary). Trials: SKYLIGHT 1-4, OASIS 1-4. TGA/PBS status changes quickly for this class — verify at tga.gov.au, pbs.gov.au and menopause.org.au before prescribing.