01. Title: Early Post-Marketing Safety Profile of Fezolinetant in FAERS: A Disproportionality Analysis With Emphasis on Hepatotoxicity

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Background: Fezolinetant is a nonhormonal neurokinin-3 receptor antagonist approved for moderate-to-severe vasomotor symptoms of menopause. Recent post-marketing safety communications have raised concern regarding potential liver injury, making early pharmacovigilance characterization clinically relevant.

Aim: To characterize early hepatic adverse-event signals for fezolinetant in FAERS, distinguishing biochemical liver-test abnormalities from coded clinical liver-injury events.

Methods: Raw FAERS quarterly ASCII files from 2023Q1 through 2026Q1 were analyzed. Reports were deduplicated by CASEID, retaining the most recent FDA date and case version. The primary exposure cohort included reports in which fezolinetant was coded as primary suspect (role_cod=PS); sensitivity analyses included primary or secondary suspect reports. Prespecified hepatic preferred terms were grouped into narrow clinical injury terms and broad hepatic enzyme/laboratory abnormalities. A case/non-case disproportionality analysis was performed using reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian Confidence Propagation Neural Network-derived IC025, and MGPS-style EBGM/EB05 shrinkage. Additional analyses included menopause-related active comparators, expanded hepatic-laboratory terms, top reported adverse events, quarterly reporting trends, and THER-based time-to-onset among reports with complete therapy start and event dates.

Results: Among 4,566,098 deduplicated FAERS cases, 1,761 were fezolinetant primary-suspect reports, 1,776 were PS+SS reports, and 1,939 mentioned fezolinetant in any role. The primary-suspect cohort was predominantly female (1,659; 94.2%) and mainly reported from the United States (76.0%). Serious outcomes occurred in 75 reports (4.3%), hospitalization in 49 (2.8%), and death in 2 (0.1%). Overall, 274 primary-suspect reports (15.6%) contained any prespecified hepatic term, including 249 (14.1%) broad hepatic enzyme/laboratory terms and 32 (1.8%) narrow clinical injury terms. Top reported events included drug ineffective (n=219), alanine aminotransferase increased (n=182), hepatic enzyme increased (n=171), aspartate aminotransferase increased (n=138), off-label use (n=105), headache (n=98), hot flush (n=86), and liver function test increased (n=84). All five prespecified broad hepatic laboratory terms showed strong multi-method concordance, with RORs from 11.3 to 49.1, IC025 values from 2.6 to 5.2, and EB05 values from 5.8 to 38.3. Among narrow clinical injury terms, jaundice showed a four-method signal (n=8), whereas liver injury (n=11) and hepatic failure (n=5) showed weaker signals not consistently confirmed by EB05. Drug-induced liver injury, hepatitis, hepatocellular injury, and hyperbilirubinaemia were sparse or null. Broad hepatic signals persisted in PS+SS sensitivity analysis and versus menopause-related comparator drugs. Expanded hepatic-laboratory sensitivity analysis also identified strong signals for hepatic enzyme increased, liver function test increased, gamma-glutamyltransferase increased, and blood alkaline phosphatase increased. Among reports with complete therapy and event dates, median time-to-onset for any hepatic term was 59.5 days.

Conclusion: In early raw FAERS data, fezolinetant showed a dominant hepatic laboratory signal, while coded clinical liver injury was infrequent.Findings are hypothesis-generating and cannot establish incidence, risk, or causality.

Key Words: Fezolinetant; Product Surveillance, Postmarketing; Adverse Drug Reaction Reporting Systems; Chemical and Drug Induced Liver Injury; Menopause.

Figure or Table:

Category	PT	n	ROR	95% CI	IC025
Broad enzyme/lab	Alanine Aminotransferase Increased	182	49.129	42.092–57.343	5.200
Broad enzyme/lab	Aspartate Aminotransferase Increased	138	42.305	35.513–50.396	4.991
Broad enzyme/lab	Transaminases Increased	27	17.563	11.994–25.717	3.496
Broad enzyme/lab	Blood Bilirubin Increased	25	15.002	10.097–22.290	3.249
Broad enzyme/lab	Liver Function Test Abnormal	13	11.311	6.547–19.542	2.623
Narrow clinical injury	Liver Injury	11	3.099	1.712–5.608	0.694
Narrow clinical injury	Jaundice	8	5.636	2.812–11.295	1.407
Narrow clinical injury	Hepatic Failure	5	2.603	1.081–6.263	0.038
Narrow clinical injury	Drug-Induced Liver Injury	5	1.166	0.485–2.805	-1.118
Narrow clinical injury	Hepatitis Acute	1	2.041	0.287–14.512	-1.686
Narrow clinical injury	Hepatocellular Injury	1	1.768	0.249–12.570	-1.893
Narrow clinical injury	Hyperbilirubinaemia	1	1.109	0.156–7.881	-2.566
Narrow clinical injury	Hepatitis	1	0.499	0.070–3.542	-3.718

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