Felodipine USP (FEL)

**Generic and additional names:** 3-ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

**CAS registry number:** 72509-76-3

**Molecular formula:** C\(_{18}\)H\(_{19}\)Cl\(_2\)NO\(_4\)

**Molecular weight:** 384.254

**Structure:**

![Felodipine structure](image)

**Properties:**

**State:** Solid

**Melting point:** 145° C

**Solubility:** It is a racemic mixture, insoluble in water and is freely soluble in dichloromethane and ethanol.

*Water solubility: 19.7 mg/L

**Log P:** 3.86

**Optimal human dosage:** The recommended starting dose is 5 mg once a day. Depending on the patient's response, the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than 2 weeks. The recommended dosage range is 2.5–10 mg once daily.
**Pharmacology**

**Mechanism of action:** FEL decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels. Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and results in vasodilation. The vasodilatory effects of FEL result in an overall decrease in blood pressure.

**Indication:** For the treatment of mild to moderate essential hypertension.

**Pharmacodynamics**

FEL belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type. It was widely accepted that CCBs target L-type calcium channels, the major channel in muscle cells that mediates contraction; however, some studies have shown that FEL also binds to and inhibits T-type calcium channels. T-type calcium channels are most commonly found on neurons, cells with pacemaker activity and on osteocytes. FEL also binds to calmodulin and inhibits calmodulin-dependent calcium release from the sarcoplasmic reticulum. The effect of this interaction appears to be minor. Another study demonstrated that FEL attenuates the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase (CaMPDE) by binding to the PDE-1B1 and PDE-1A2 enzyme subunits. CaMPDE is one of the key enzymes involved in cyclic nucleotides and calcium second messenger systems. FEL also acts as an antagonist to the mineralcorticoid receptor by competing with aldosterone for binding and blocking aldosterone-induced coactivator recruitment of the mineralcorticoid receptor. FEL is able to bind to skeletal and cardiac muscle isoforms of troponin C, one of the key regulatory proteins in muscle contraction. Though FEL exhibits binding to many
endogenous molecules, its vasodilatory effects are still thought to be brought about primarily through inhibition of voltage-gated L-type calcium channels. Similar to other DHP CCBs, FEL binds directly to inactive calcium channels stabilizing their inactive conformation. Since arterial smooth muscle depolarizations are longer in duration than cardiac muscle depolarizations, inactive channels are more prevalent in smooth muscle cells. Alternative splicing of the alpha-1 subunit of the channel gives FEL additional arterial selectivity. At therapeutic sub-toxic concentrations, FEL has little effect on cardiac myocytes and conduction cells.

**Pharmacokinetics**

*Absorption:* It is completely absorbed from the gastrointestinal tract; however, extensive first-pass metabolism through the portal circulation results in a low systemic availability of 15%. Bioavailability is unaffected by food.

*Distribution:* Animal studies have demonstrated that FEL crosses the blood-brain barrier and the placenta. It is 99%, primarily to the albumin fraction.

*Metabolism:* FEL undergoes hepatic metabolism primarily via cytochrome P450 3A4. Six metabolites with no appreciable vasodilatory effects have been identified.

*Elimination:* Although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.

*Half-life:* 17.5-31.5 h in hypertensive patients; 19.1-35.9 h in elderly hypertensive patients; 8.5-19.7 in healthy volunteers.

**Human adverse reactions**

Flushing, headache, peripheral oedema, tachycardia, palpitation, dizziness, fatigue. Ankle swelling may occur. Hyperplasia, rash, pruritus. Gingival enlargement, angina, angioedema, decreased libido, insomnia, irritability in patients with pronounced gingivitis or periodontitis.