THE NORTHERN HOSPITAL

# FELODIPINE

*"Fabiola", copy of a lost original; oil in canvas, 1885, by Jean-Jacques Henner, (collection of AM Hayes)*

*It is harder for us to part with arrogance than with gold and gems. For, even though we may throw these away, we plume ourselves sometimes on a meanness that is really ostentatious, and we make a bid with a saleable poverty for the popular applause. But a virtue that seeks concealment and is cherished in the inner consciousness appeals to no judgment but that of God…..*

*With her own hand she would offer food and give water to a living corpse…..*

*And because at the very outset there is a rock in the path and she is overwhelmed by a storm of censure, for having forsaken her first husband and having taken a second, I will not praise her for her conversion till I have first cleared her of this charge. So terrible then were the faults imputed to her former husband that not even a prostitute or a common slave could have put up with them….*

*St. Jerome, eulogy to Fabiola, 399 A.D*

*Fabiola came from a an ancient and wealthy Roman noble family, and so life should have been good for her. But it was not. She was married to a man so callous and so vicious, that she took the rare and astonishingly courageous step for a woman of the Fourth century AD of divorcing her husband as she had a right to according to Roman law. People could sympathize with her case, however when she remarried another man, before the death of her first brutal husband, she was ostracized without mercy, as this action was against the religious laws of the recently Christianized Roman state. She did however, have an unlikely sympathizer and ally. One of the most revered early fathers, of the Church, St Jerome had came to Rome in 382 A.D. Fabiola was not one of the admiring thongs that came to hear him preach, but she did take quiet comfort from his teachings. On hearing of her plight, in an astonishingly progressive pronouncement for the early Church, Jerome declared that if men were able to divorce their wives, then women should be able to do the same to their husbands, just as Roman secular law stated. "Whatever is ordained for men", Jerome announced in support of Fabiola, "consequently also applies to women!"*

*On the sudden death of her second husband, her only solace came from the new Christianity. She decided to renounce her worldly possessions and to dedicate herself to a life of serving the destitute, the poor and the sick. In 395 AD she went on pilgrimage to Bethlehem, under the direction of Jerome. But things were difficult in Jerusalem, as the Bishop there, was in theological dispute with her patron. When the Huns began raiding the Eastern provinces, Jerusalem became too dangerous and so Fabiola returned to Rome, where she took up nursing and founded a house for the sick, in essence the first public hospital in Rome, indeed in the Western world. "With her own hand, Jerome wrote, "she would offer food and give water to a living corpse…" Fabiola died of an unknown ailment at an unknown age, in 399 A.D. Jerome left a heartfelt and touching eulogy to her for posterity.*

*Fabiola today is considered a Saint of the early Catholic church, to many she is seen as the patron saint not only to women divorcees but also to nurses. Her story would have remained somewhat obscure, if not for a famous imaginary portrait made of her by a lesser known French Artist of the Nineteenth century, by the name of Jean-Jacques*

*Henner. He produced the work in 1885, and it immediately struck a chord with fellow Artists, who produced many copies and variations of it, as popular demand for the image soared. It's impossible to say what Artistic influences Henner had, but his work echoes that of "The Vestal", oil on canvas, c. 1882-83 by the great Lord Frederick Leighton. During an auction in 1912, seven years after Henner's death, the painting was lost, possibly stolen. It has not been seen again for over a century. This tragedy did not however dampen the spirit or legacy of Henner's "Fabiola", and Artists across the world continued to reproduce his masterpiece, even though today the only distant memory of it lies in a on old black and white photograph, taken some time at the "fin de (Nineteenth) siècle".*

*Henner's "Fabiola" lived on into the Twenty First century via Belgian-born, Mexican-based artist Francis Alÿs. Obsessed by the story of Fabiola and the lost portrait he amassed, over 15 years, an astonishing personal collection of over 300 copies by various Artists. In 2008 he mounted a traveling exhibition of these that went to many prestigious galleries including the Hispanic Society of America in New York City, the in Los Angeles County Museum of Art, Los Angeles, the National Portrait Gallery in London, and the Byzantine Fresco Chapel of the Menil Collection in Houston, Texas.*

*When big Pharma finds a winning formula that strikes a popular chord there will, like Henner's, St. Fabiola, be no end of "reproductions" that follow, even though the original prototype may be long lost. The origins of the calcium channel blockers reach back to the mid 1960s. Today there are many reproductions of these, among the most popular includes the agent felodipine.*

*A sample of Francis Alÿs' collection of "St. Fabiolas"; installation. National Portrait Gallery, London, 2009.*

# FELODIPINE

## Introduction

**Felodipine** is a **dihydro-pyridine** calcium channel blocking agent.

It is principally used for:

1 Chronic hypertension

2. Angina.

The dihydropyridine calcium blocking agents act mainly on arteriolar smooth muscle to reduce peripheral vascular resistance and blood pressure. They have minimal effect on myocardial cells.

**See also separate Document on:**

- **Calcium Channel Blocker Overdose (Toxicology Folder)**

## History

In 1883 Ringer reported, from a series of experiments on isolated heart, that calcium was required for the maintenance of cellular activity.

In 1901, Stiles extended this observation to smooth muscle contraction.

Sixty years later, Kamada in Japan (Kamada and Kinosita, 1943) and Heilbrunn in the United States (Heilbrunn and Wiercinski, 1947) elucidated the mechanism of intracellular calcium for muscle contraction.

Today calcium is known to be involved in a wide range of cellular processes including a ubiquitous role as an intracellular second messenger. Studies on the pharmacology of calcium function were initiated in the 1960s and the German pharmacologist and physiologist **Albrecht Fleckenstein** (1917 - 1992) developed the first calcium channel blockers in 1964.

The first therapeutic agents began to be introduced into clinical practice in the 1970s

Felodipine was introduced into clinical practice in 1988.

## Chemistry

**Felodipine** is a **dihydro-pyridine** calcium channel blocking

## Classification

Calcium channel blockers can be classified into two principle groups:

1. Dihydropyridines:

The dihydro-pyridines act mainly on **arteriolar smooth muscle** to reduce peripheral vascular resistance and BP.

They have *minimal* effect on myocardial cells.

*Examples include:*

- Amlodipine
- **Felodipine**
- Lercanidipine
- Nifedipine
- Nimodipine
- Clevidipine

2. Non-dihydropyridines:

*Non-dihydropyridines*: act primarily on **cardiac** and **arteriolar** smooth muscle.

They reduce cardiac contractility, heart rate and conduction, with verapamil having the greater effect.

Diltiazem has a greater effect on arteriolar smooth muscle than verapamil.

*Examples include:*

- Verapamil
- Diltiazem

## Preparation

Felodipine as:

Extended release tablets:

- 2.5 mg, 5 mg, 10 mg.

Fixed dose combinations:

- Fixed dose combinations with ramipril are also available.

## Mechanism of Action

Calcium channel blockers block the inward current of calcium into cells in vascular smooth muscle, myocardium and cardiac conducting system via the L-type calcium channels.

They act on coronary arteriolar smooth muscle to reduce vascular resistance and myocardial oxygen requirements, relieving angina symptoms.

*Dihydropyridines* such felodipine act mainly on arteriolar smooth muscle to reduce peripheral vascular resistance and blood pressure. They have minimal effect on myocardial cells.

*Non-dihydropyridines* (i.e. diltiazem and verapamil) act on cardiac and arteriolar smooth muscle. They reduce cardiac contractility, heart rate and conduction, with verapamil having the greater effect. Diltiazem has a greater effect on arteriolar smooth muscle than verapamil.

## Pharmacodynamics

The acute haemodynamic effect of felodipine is to reduce total peripheral resistance which leads to a decrease in blood pressure and a slight and transient reflex increase in heart rate and cardiac output.

A reduction in blood pressure is usually evident 2 hours after an initial oral dose of the extended release preparation.

The effect lasts for at least 24 hours at steady state.

## Pharmacokinetics

### *Absorption:*

- Felodipine is given orally.

  It is completely absorbed from the GIT

  Due to pre-systemic i.e. “first pass, metabolism of felodipine however, the *bioavailability* of the extended release dosage form is only about 20%.

### *Distribution:*

- Plasma protein binding of felodipine is high at approximately 99 %.
- The Vd at steady state is approximately 10 L/kg.
- Felodipine crosses the human placenta.

- It is likely that felodipine is excreted into human breast milk, but only in small amounts.

*Metabolism and excretion:*

- Felodipine is extensively metabolised in the liver by cytochrome P450 3A4 (CYP3A4).

  All identified metabolites are inactive.

- Half life varies from 4 to 24 hours

## Indications

Felodipine is principally used for:

1 Chronic hypertension

2. Angina.

## Contraindications/ Precautions

For the calcium channel blockers as a class include:

1. Hypotension, (contraindicated)

   - In general terms, a systolic BP < 90 mm Hg.

2. Cardiogenic shock, (contraindicated)

3. Bradycardia, (contraindicated)

4. Sick sinus syndrome (contraindicated)

5. Conduction delays, (contraindicated)

   - Second or third degree atrioventricular block without pacemaker,

6. Significant LV failure, (contraindicated)

   - Calcium channel blockers may further depress myocardial function in patients with systolic heart failure.

     Verapamil and diltiazem are generally contraindicated (unless under specialist supervision); dihydropyridines may be used with caution.

7. AF in patients with an accessory bypass tract, (contraindicated).

- e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes

8. VT, (contraindicated)

9. **Calcium channel blocker** and **Beta Blocker** interaction:

   - The combination of beta blocker and calcium channel blocker *frequently* causes conduction delay problems in the *elderly*, especially in the presence of *renal impairment.*

   - Calcium antagonists of the verapamil type should **not** be given by intravenous administration to patients treated with beta-blockers

10. **Grapefruit juice** should be avoided:

    - Grapefruit juice is a well documented **inhibitor of the CYP - 3A4 enzyme**, which is involved in the metabolism of many commonly prescribed drugs.

      By inhibiting the CYP - 3A4 enzyme, it can result significantly increased levels of verapamil in the blood and result in toxicity.

11. Known hypersensitivity

12. Caution in liver impairment.

*Pregnancy*

Felodipine is a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations.

These effects may be reversible. Specialised texts should be consulted for further details.

Maternal use of calcium channel blockers in early pregnancy has not been associated with an increased risk of major malformations.

Three case reports of maternal treatment with felodipine throughout pregnancy for chronic hypertension did not describe adverse fetal effects.

However, treatment-induced falls in maternal blood pressure may potentially cause fetal hypoxia or adversely affect fetal growth.

If felodipine is the medicine of choice, use the lowest effective dose and closely monitor maternal blood pressure.

*Breast feeding*

Reports describing the use of felodipine during breastfeeding have not been located.

Felodipine is likely to be excreted into the breast milk, but in only very small amounts, as the medicine is highly protein bound.

If felodipine is the medicine of choice, monitor the breastfed infant for potential adverse effects such as hypotension and bradycardia.

## Adverse Effects

In general the dihydropyridines have more pronounced vasodilatory effects than diltiazem and verapamil.

Verapamil, (and to a lesser extent, diltiazem), reduce cardiac contractility, heart rate and conduction.

The important adverse effects include:

1. Hypotension

2. Negative inotropy

2. Bradycardia

3. Conduction delays

4. Myasthenia-like neuromuscular disease:

    - Calcium channel blockers in general may increase risk of muscle weakness and respiratory depression (most case reports are with verapamil).

*Less severely:*

5. Peripheral edema, (though *dihydropyridines* more commonly cause peripheral oedema due to redistribution of extracellular fluid - rather than fluid retention)

    - Note that this does *not* respond to treatment with diuretics, which may put patient at risk of volume depletion.

6. Constipation

## Dosing

These tablets are extended release preparations and so should be swallowed whole and not crushed or chewed.

Usual dosing in **adults** is:

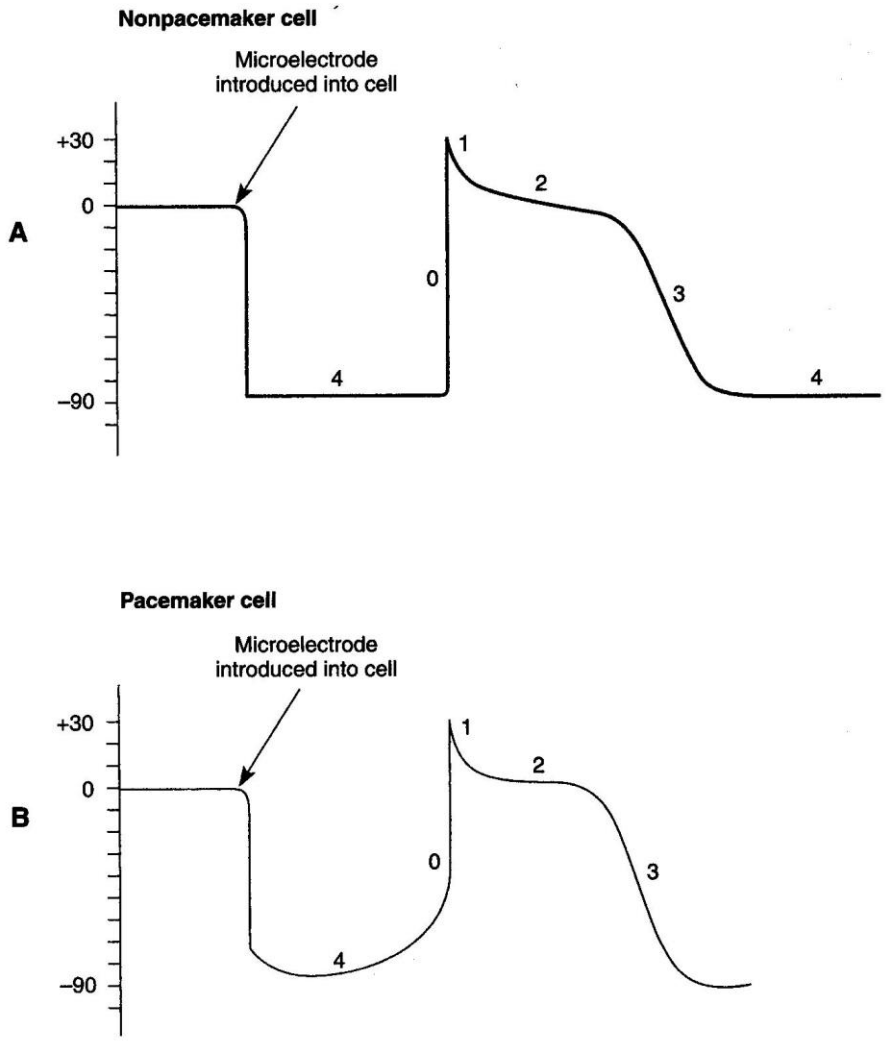
- Initially 5 mg once daily.
- Maintenance dose 5-10 mg once daily
- Maximum dose is 20 mg once daily.

Elderly patients, or those with hepatic impairment:

- Initially 2.5 mg once daily.

## Appendix 1

*Myocardial Action Potentials:*




*The pattern of action potentials from non-pacemaker cardiac cells and pacemaker cardiac cells.*

*References*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3. Felodipine in MIMs 1 April 2013.

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