4. Drug profile

4.1 Almotriptan malate

i Chemical structure

![Chemical structure of Almotriptan malate]

ii Chemical name

1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol5-yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate

iii Molecular formula

\( C_{17}H_{25}N_{3}O_{2}S-C_4H_6O_5 \)

iv Molecular weight

469.56 da

v Category

Anti-migraine drug, 5-HT1B/1D receptors agonist

vi Physical and chemical property

- **Physical appearance**: white to slightly yellow crystalline powder
- **Melting point**: 170-172°C
- **Solubility**: soluble in water, freely soluble in methanol and dichloromethane
- **Half life**: Almotriptan has a mean half-life of 3 to 4 hrs
- **Loss on drying**: 2% w/w
- **LogP / Hydrophobicity**: 1.6
vii Pharmacokinetics

※ Absorption
The absolute bioavailability of almotriptan is about 70%, with peak plasma levels occurring 1 to 3 hrs after administration; food does not affect pharmacokinetics.

※ Distribution
Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180 to 200 ltrs.

※ Metabolism
Almotriptan is metabolized by two major and one minor pathway. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose), and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin monoxygenase is the minor route of metabolism. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

※ Excretion
Almotriptan is eliminated primarily by renal excretion (about 75% of the oral dose), with approximately 40% of an administered dose excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

※ Mechanism of action
The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-HT1B/1D receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways.

※ Dose
6.25 to 12.5 mg. If headache returns, may repeat dose after 2 hrs (max, 2 doses per 24 hrs).
**Adverse effect/ toxicity**

The following adverse reactions are: Serious cardiac reactions, including myocardial infarction, have occurred following the use of AXERT Tablets. These reactions are extremely rare and most have been reported in patients with risk factors predictive of CAD. Reactions reported, in association with triptans, have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

**Contraindications**

Ischemic heart disease (eg, angina pectoris, history of MI, documented silent ischemia); symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm (including Prinzmetal variant angina), or other significant underlying CV disease; cerebrovascular syndromes, including but not limited to stroke of any type as well as transient ischemic attacks; peripheral vascular disease, including but not limited to ischemic bowel disease; uncontrolled hypertension; use within 24 hrs of treatment with another 5-HT1 agonist or ergotamine-containing or ergot-type medication; hemiplegic or basilar migraine; hypersensitivity to any component of the product.

**Marketed formulation**

AXERT Tablets are available as 6.25 mg and 12.5 mg strength of almotriptan.