ANNEXURE 1. DRUG AND IM’s PROFILE

PHENYTOIN (PHY)

Phenytoin sodium is a commonly used as antiepileptic. Phenytoin acts to suppress the abnormal brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage-gated sodium channels. A side from seizures, it is an option in the treatment of trigeminal neuralgia. It is used for oral and parenteral administration.

IUPAC Name: 5,5-diphenylimidazolidine-2,4-dione.
Chemical formula: C_{15}H_{12}N_{2}O_{2}
Molecular Weight: 252.268 g/mol
t1/2: 6-24 hrs
Protein: 90%
Bioavailability: 70-100% oral, 24.4% for rectal and IV administration
Solubility: Slightly soluble in acetone and ethanol, insoluble in water.
Dose: 300 mg daily in divided doses

Indication and Dosage

Oral

Epilepsy
Adult: Initially, 3-4 mg/kg daily as single dose or in divided doses. Alternatively, 150-300 mg increased gradually to 600 mg daily if necessary. Maintenance: 200-500 mg daily.
Child: Initially, 5 mg/kg daily in 2-3 divided doses. Maintenance: 4 - 8 mg/kg daily in divided dose.
Intravenou
s
Tonic-clonic epilepticus
Adult: Adjunctive therapy with a benzodiazepine (e.g. diazepam): 10-15 mg/kg by slow inj or intermittent infusion at a max rate of 50 mg/min. Maintenance: 100 mg IV (or orally) given 6-8 hr.
Child: Neonates: 20 mg/kg as a loading dose, then 2.5-5 mg/kg bid; 1 mth-12 yr: 18 mg/kg as a loading dose, then 2.5-5 mg/kg bid; >12 yr: 18 mg/kg as a loading dose, then up to 100 mg 3-4 times daily.

Contraindications
Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

Side effects
Sedation, impaired memory, slurred speech, nystagmus, decreased coordination, confusion, dizziness and headache.

Adverse reactions
Hypersensitivity, lack of appetite, headache, dizziness, tremor, transient nervousness, insomnia, GI disturbances (e.g. nausea, vomiting, constipation), tenderness and hyperplasia of the gums, acne, hirsutism, coarsening of the facial features, rashes, osteomalacia. Phenytoin toxicity as manifested as a syndrome of cerebellar, vestibular, ocular effects, notably nystagmus, diplopia, slurred speech, and ataxia; also with mental confusion, dyskinesias, exacerbations of seizure frequency, hyperglycaemia. Solutions for inj may cause local irritation or phlebitis. Prolonged use may produce subtle effects on mental function and cognition, especially in children. Potentially Fatal: Toxic epidermal necrolysis, Stevens-Johnson syndrome.

Drug Interactions
- Effects with other sedative drugs or ethanol may be potentiated.
- Enhances toxic effects of paracetamol, lithium. Increased risk of osteomalacia with acetazolamide.
- Increases metabolism of anti arrhythmics, anticonvulsants, antipsychotics, betablockers, calcium channel blockers, chloramphenicol, corticosteroids, doxycycline, oestrogens, HMG-CoA reductase inhibitors, methadone, theophylline, TCAs. Decreases levels/effects of clozapine, ciclosporin, tacrolimus, CYP2B6 substrates (e.g. bupropion, selegiline), CYP2C8 substrates (e.g. amiodarone), CYP2C9 substrates (e.g. celecoxib), CYP2C19 substrates (e.g. citalopram), CYP3A4 substrates (e.g. benzodiazepines), digoxin, itraconazole, levodopa, neuromuscular-blocking agents, thyroid hormones, topiramate.
- Increases levels/effect of dopamine, ticlopidine.
- Valproic acid may displace phenytoin from binding sites; and affect phenytoin serum concentrations.

**Storage**

BENZIL (BZL)
Benzil is a standard building block in organic synthesis. It condenses with amines to give diketimines ligands. A classic organic reaction of benzil is the benzilic acid rearrangement, in which base catalyses the conversion of benzil to benzilic acid. This reactivity is exploited in the preparation of the drug phenytoin.

![Benzil Chemical Structure]

Molecular weight : 210.23 g mol⁻¹
Chemical formula : C₁₄H₁₀O₂
Solubility : Practically insoluble in water, freely soluble in alcohol, ether, chloroform, toluene, ethylacetate, benzene & nitrobenzene.
Applications : Most benzil is consumed for use in the free-radical curing of polymer networks. Ultraviolet radiation decomposes benzil, generating free radical species within the material, promoting the formation of cross-links.
WARFARIN (WAR)

Warfarin is an anticoagulant. It is used for oral or intravenous administration

![Chemical Structure of Warfarin](image)

- **IUPAC name**: 3-(α-acetonylbenzyl)-4-hydroxycoumarin
- **Chemical formula**: C₁₉H₁₆O₁₄
- **Molecular Weight**: 308.33 g/mol
- **t½**: 40 hrs
- **Protein**: 99.5%
- **Bioavailability**: 100%
- **Solubility**: soluble in acetone, insoluble in water.
- **Dose**: 5mg/day

**Indications**: Treatment and prevention of venous thromboembolism.

**Dosage**

**Adult**: PO/IV Initial: 5 mg/day. Rapid anti-coagulation: Initial: 10 mg/day for 2 days. Adjust subsequent doses based on prothrombin time/INR. Usual maintenance: 2-10 mg/day.

**Contraindications**

Hypersensitivity; haemorrhagic tendencies or blood dyscrasia; recent surgery; peptic ulcer; severe hypertension; bacterial endocarditis; cerebrovascular disorders; psychosis; senility; aneurysms; pericarditis; pericardial effusion; eclampsia; pre-eclampsia; threatened abortion; alcoholism; severe renal and hepatic impairment; pregnancy.
Side effects

- Blood in the urine.
- Bleeding gums.
- Unusual bleeding are potentially serious warfarin side effects that should be reported to a healthcare provider right away.
- Careful monitoring (using a blood test) can help reduce the risk of many of these serious problems.
- Some of the side effects that are merely bothersome and usually not dangerous include lethargy and weakness, taste changes and hair loss.

Adverse reactions: Hypersensitivity, rash, alopecia, diarrhoea, drop in haematocrit, purple toes syndrome, skin necrosis, jaundice, nausea, vomiting, hepatic dysfunction, pancreatitis, increased LFT.

Potentially Fatal: Haemorrhage.

Drug Interactions

- Potentially Fatal: Acute alcoholism, allopurinol, NSAIDs, anabolic steroids, amiodarone, propafenone, quinidine, chloramphenicol, ciprofloxacin, cotrimoxazole, erythromycin, metronidazole, ofloxacin, sulfonamides, azithromycin, clarithromycin, norfloxacin, tetracyclines, SSRI, fluconazole, itraconazole, miconazole, ketoconazole, proguanil, cisapride, ifosfamide, disulfiram, piracetam, zafirlukast, interferonα, isoniazid, tramadol, glucagon, doxycycline, propylthiouracil, danazol, flutamide, tamoxifen, clofibrate, simvastatin, cimetidine, sulfinpyrazone enhance anticoagulant effect of warfarin.
- Drugse.g., rifampicin, carbamazepine, phenobarbital, barbiturates, bosentan, nafcillin, azathioprine menthol, primidone, griseofulvin andaminoglutethimide, oral contraceptives containing oestrogens, corticosteroids, sucralfate, vit K as well as chronic alcoholism reduce anticoagulant effect.
- Cholestyramine may reduce anticoagulant effect, avoid admin of warfarin 1 hr before or 4-6 hr after cholestyramine.
BENZALACETONE (BAZ)
Benzylideneacetone is the organic compound. Although both cis- and trans-isomers are possible for the α,β-unsaturated ketone, only the trans isomer is observed.

**Structural formula**

![Structural formula]

IUPAC name : 4-phenyl-3-Buten-2-one
Molecular formula : C\textsubscript{10}H\textsubscript{10}O\textsubscript{2}
Molecular weight : 146.19 g mol\textsuperscript{-1}
Solubility : Soluble in diethyl ether, acetone, benzene, chloroform ethanol. Insoluble in cold water, hot water.
NICERGOLINE (NIC)

Nicergoline (marketed under the trade name Sermion) is an ergot derivative used to treat senile dementia and other disorders with vascular origins. It has been found to increase mental agility and enhance clarity and perception. It decreases vascular resistance and increases arterial blood flow in the brain, improving the utilization of oxygen and glucose by brain cells. It has similar vasoactive properties in other areas of the body, particularly the lungs. It is used for vascular disorders such as cerebral thrombosis and atherosclerosis, arterial blockages in the limbs, Raynaud's disease, vascular migraines, and retinopathy.

Structure:

Chemical name : [(8β)-10-methoxy-1,6-dimethylergolin-8-yl] Methyl bromopyridine 3- carboxylate

Molecular formula : C_{24}H_{28}BrN_{3}O_{3}

Molecular weight : 484.386 g/mol.
Bio availability : < 5%
Protein binding : > 90%
Half life : 13-20 hrs

**Indication and Dosage**

**Oral:** For vascular diseases, mental detoriation associated with cerebro vascular insufficiency 10 mg 3 times a day. Maintenance dose 5-10 mg 3 times/day. Maximum dose 60 mg/day in divided doses.

**IV:** For vascular diseases, mental detoriation associated with cerebro vascular insufficiency 4-8 mg via infusion.

**IM:** For vascular diseases, mental detoriation associated with cerebro vascular insufficiency 2-4 mg twice daily.

**Contraindications**

Persons suffering from acute bleeding myocardial infarction (heart conditions), hypertension, bradycardia or using alpha or beta receptor agonist should consult their physician before use.

Although toxicological studies have not shown to have any teratogenic effect the use of this medicine during pregnancy should be limited to those cases where it is absolutely necessary. Nicergoline is considered unsafe in porphyria.

**Adverse effects**

The side effects of nicergoline are limited nausea, hot flushes, mild gastric upset, hypotension and dizziness at high doses causes bradycardia increased apatite, agitation, diarrhea and perspiration have been known to occur. A single case of acute interstitial nephritis have been occurred.

**Mechanism of Action**

Nicergoline is an ergot alkaloid that acts as a potent and selective alpha-1A adrenergic receptor agonist. The primary action of nicergoline is to increase arterial blood flow by vaso dilation. Furthermore it is shown that nicergoline inhibits platelet aggregation. Studies have shown that nicergoline also increases nerve growth factor in aged brains.
Drug Interactions

Nicergoline is known to enhance the cardiac depressive effects of propranolol. At high doses it is advisable to seek one’s physician’s guidance if combined with potent vasodilators such as bromocriptine, vincocetine.
5-BROMO NICOTINIC ACID (5BNA)

Molecular weight : 202.01 g/mol
Chemical formula : C₆H₄BrNO₂
Storage temperature : Store in a tightly closed container. Store in a cool, dry, well ventilated area away from incompatible substances.
Stability : Stable at room temperature in closed containers and normal storage and handling conditions.
ANNEXURE 2. LIST OF PAPERS PRESENTED

1. **M.R. Jeyaprakash, V.Sireesha, M. Sravanthi and S.N. Meyyanathan.** “Genotoxicity Study Of Benzil By AMES Test” 64th Indian Pharmaceutical Congress, 7-9 December 2012, Chennai.


4. **M.R. Jeyaprakash, B. Babu and S.N. Meyyanathan.** “Method development and validation for the estimation of %bromo nicotinic acid impurity in nicergoline by LCMS” 65th Indian Pharmaceutical Congress, AMITY University, Noida, Delhi, 20-22 December 2013

5. **M.R. Jeyaprakash, B. Babu and S.N. Meyyanathan** “Method development and validation for the estimation of benzil impurity in phenytoin tablet dosage form by LCMS” National seminar on quality Pharmacy education expected by industries from academia, Arulmigu Kalasalingam College of Pharmacy, Krishnan Koil, Tamilnadu, 14-15 March 2014


7. Received “Best Poster Presentation Award” for the paper entitled “Method development and validation for the estimation of benzil impurity in phenytoin tablet dosage form by LCMS” National seminar on quality Pharmacy education expected by industries from academia, Arulmigu Kalasalingam College of Pharmacy, KrishnanKoil, Tamilnadu, 14-15 March 2014
ANNEXURE 3. LIST OF PUBLICATIONS


2. Paper entitled “Development And Validation For The Estimation Of Bezalacetone Impurity In Warfarin Formulations By RP-HPLC" Communicated to Journal of Pharmacy Research (Under Review)