

Background for Health Care Provider:

Primidone is almost completely absorbed, and does not bind significantly to plasma proteins. Primidone undergoes metabolism by the liver (mostly) and kidney (partially) to two metabolites: phenobarbital and phenylethylmalonamide.

Since both primidone and phenobarbital have antiepileptic activity, its effectiveness is a consequence of the plasma serum levels of both of these forms. Therefore, phenobarbital's metabolism and excretion must also be taken into consideration when considering the drug interactions of primidone. Phenobarbital undergoes extensive metabolism by the cytochrome P450 isoforms CYP2C9 and CYP2C19. Both primidone and its metabolites are primarily excreted via the kidney.

Many of the interactions that occur are due to alterations in the biotransformation of primidone to phenobarbital. Additionally, there are all of the interactions seen with phenobarbital. Many drugs have been reported to interact with phenobarbital, resulting in lack of effectiveness or side effects from phenobarbital or the other drug it is reacting with. Phenobarbital is also a very potent broad spectrum inducer of various compounds' metabolism.

Since primidone and phenobarbital are both extensively metabolized, most of the drug interactions have been shown to occur due to changes in metabolism. Additionally, many other CYP inducers increase the transformation of primidone to phenobarbital. Primidone and phenobarbital induce many CYP450 enzymes, which could cause decreased blood levels for drugs metabolized by enzymes in the liver. Drugs that inhibit CYP2C9 and CYP2C19 have been shown to increase blood levels of phenobarbital while those that induce these CYP enzymes have been shown to decrease phenobarbital blood levels. Both of the CYP450s that are responsible for metabolizing phenobarbital are expressed polymorphically in humans and genetic defects in expression of these could cause toxicity in these patients with normal phenobarbital doses. Interactions can also occur when renal excretion is altered. Since primidone is a weak acid, excretion could be altered by changes in the pH of the urine.

Effect of Other Drugs on Primidone/Phenobarbital Serum Levels:

Decrease Primidone/Phenobarbital Serum Levels:

- Antacids
- Acetazolamide

Increase Primidone/Phenobarbital Serum Levels:

- Carbamazepine
- Dexmethylphenidate
- Felbamate
- Fosphenytoin
- Phenytoin
- Primidone
- Valproic Acid

Effect of Primidone/Phenobarbital on Other Drugs' Serum Levels:

Increase Other Drug Serum Levels:

- No known clinically significant interactions

Decrease Other Drug Serum Levels:

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|-------------------|------------------------------|
| • Anisindione | • Nifedipine |
| • Chloramphenicol | • Oral Contraceptives |
| • Corticosteroids | • Propafenone |
| • Cyclosporine | • Protriptyline |
| • Dicumarol | • Quinidine |
| • Disopyramide | • Theophylline |
| • Doxycycline | • Tiagabine |
| • Folic Acid | • Tri-cyclic antidepressants |
| • Griseofulvin | • Verapamil |
| • Lamotrigine | • Warfarin |
| • Methadone | |

Variable effects on Serum Levels:

- Phenytoin

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