VITAMIN K1 is a family of phylloquinones that contains a ring of 2-methyl-1,4-naphthoquinone and an isoprenoid side chain. Members of this group of vitamin K1 have only one double bond on the proximal isoprene unit. Rich sources of vitamin K1 include green plants, algae, and photosynthetic bacteria. Vitamin K1 has antihemorrhagic and prothrombogenic activity.

Vitamin K is a family of fat-soluble compounds with a common chemical structure based on 2-methyl-1,4-naphthoquinone

Metabolite Description from Human Metabolome Database (HMDB)
2 3D Conformer

- Search
- Download
- Get Image

Magnify

- Show Hydrogens
- Show Atoms
- Animate

from PubChem
### 3 Names and Identifiers

#### 3.1 Computed Descriptors

##### 3.1.1 IUPAC Name

2-methyl-3-[(E,7R,11R)-3,7,11,15-tetramethylhexadec-2-enyl]naphthalene-1,4-dione  
› from PubChem

##### 3.1.2 InChI

› from PubChem

##### 3.1.3 InChI Key

MBWXNTAXLNYFJB-NKFFZRIASA-N  
› from PubChem

##### 3.1.4 Canonical SMILES

CC1=C(C(=O)C2=CC=CC=C2C1=O)CC=C(C)CCCC(C)CCCC(C)CCCC(C)C  
› from PubChem

##### 3.1.5 Isomeric SMILES

CC1=C(C(=O)C2=CC=CC=C2C1=O)C/C=C(\C)CCCC[C@H](C)CCCC[C@H](C)CCCC(C)C  
› from PubChem

#### 3.2 Molecular Formula

C\textsubscript{31}H\textsubscript{48}O\textsubscript{2}  
› from PubChem

#### 3.3 Other Identifiers

##### 3.3.1 CAS

84-80-0
3.3.2 EC Number

201-564-2

234-330-3

234-408-7

279-052-3

3.3.3 NSC Number

760373

3.3.4 UNII

S5Z3U87QHF

3.3.5 Wikipedia

<table>
<thead>
<tr>
<th>Title</th>
<th>(E)-phytonadione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>chemical compound</td>
</tr>
</tbody>
</table>

3.3.6 Wikipedia

6 di 57

12/01/18, 11:36
### 3.4 Synonyms

#### 3.4.1 MeSH Entry Terms

1. Aquamephyton
2. Konakion
3. Phyllohydroquinone
4. Phylloquinone
5. Phytomenadione
6. Phytonadione
7. Vitamin K 1
8. Vitamin K1

└ from MeSH

#### 3.4.2 Depositor-Supplied Synonyms

| 2. phytonadione | 12. Konakion | 22. trans-Phylloquinone |
| 5. Phytylmenadione | 15. Kephton | 25. UNII-S5Z3U87QHF |
| 7. Phytomenadione | 17. Synthex P | 27. Fitomenadiona |
| 8. alpha-Phylloquinone | 18. VITAMIN K | 28. Phyllochinonum |
| 9. 3-Phytylemenadione | 19. Mono-Kay | 29. Phytomenadionum |
| 10. 2-Methyl-3-phytyl-1,4-naphthoquinone | 20. Combinal K1 | 30. Phytonadionum |

└ from PubChem
## 4 Chemical and Physical Properties

### 4.1 Computed Properties

<table>
<thead>
<tr>
<th>Property Name</th>
<th>Property Value</th>
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<tbody>
<tr>
<td>Molecular Weight</td>
<td>450.707 g/mol</td>
</tr>
<tr>
<td>Hydrogen Bond Donor Count</td>
<td>0</td>
</tr>
<tr>
<td>Hydrogen Bond Acceptor Count</td>
<td>2</td>
</tr>
<tr>
<td>Rotatable Bond Count</td>
<td>14</td>
</tr>
<tr>
<td>Complexity</td>
<td>696</td>
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<tr>
<td>CACTVS Substructure Key Fingerprint</td>
<td>AAADcfB4MAAAAAAAAACBBAAAGgAAAAADQSAmAAyAI</td>
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<td></td>
<td>AAAAClAqBAAACAAAkAAAlAEAMGlIDKAFRCA</td>
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<tr>
<td></td>
<td>IQAggAlYcJMCogAAAAAQAAAAAACAAPA =</td>
</tr>
<tr>
<td>Topological Polar Surface Area</td>
<td>34.1 Å²</td>
</tr>
<tr>
<td>Monoisotopic Mass</td>
<td>450.35 g/mol</td>
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<tr>
<td>Exact Mass</td>
<td>450.35 g/mol</td>
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<tr>
<td>XLogP3-AA</td>
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<td>Compound Is Canonicalized</td>
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<tr>
<td>Formal Charge</td>
<td>0</td>
</tr>
<tr>
<td>Heavy Atom Count</td>
<td>33</td>
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<tr>
<td>Defined Atom Stereocenter Count</td>
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</tr>
<tr>
<td>Undefined Atom Stereocenter Count</td>
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</tr>
<tr>
<td>Defined Bond Stereocenter Count</td>
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<tr>
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</tr>
<tr>
<td>Isotope Atom Count</td>
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</tr>
<tr>
<td>Covalently-Bonded Unit Count</td>
<td>1</td>
</tr>
</tbody>
</table>

*from PubChem*

### 4.2 Experimental Properties

#### 4.2.1 Physical Description

**Solid**

*from Human Metabolome Database (HMDB)*
Liquid

from Human Metabolome Database (HMDB)

4.2.2 Color

Yellow viscous oil


from HSDB

LIGHT-YELLOW SOLIDS OR OILS


from HSDB

Pale yellow oil or yellow crystals


from HSDB

Clear, yellow to amber, viscous, odourless liquid


from HSDB

4.2.3 Odor

Odorless


from HSDB

4.2.4 Boiling Point

142.5 °C at 1.00E-03 mm Hg

PhysProp

140-145 deg C @ 0.001 mm Hg


from HSDB

4.2.5 Melting Point
-20 °C

PhysProp


-20 °C


-20 °C

from Human Metabolome Database (HMDB)

4.2.6 Solubility

Water Solubility

Insoluble in water

Insoluble in water; sparingly soluble in methanol; sol in ethanol; sol in acetone, benzene, petroleum ether, hexane, and dioxane; sol in chloroform, and other fat solvents; sol in vegetable oils


SOL IN FATS


5.92e-05 g/L

from Human Metabolome Database (HMDB)

4.2.7 Density

0.964 @ 25 deg C/25 deg C


4.2.8 LogP

9.3

from DrugBank, Human Metabolome Database (HMDB)

4.2.9 Stability
STABLE TO AIR & MOISTURE, BUT DECOMP IN SUNLIGHT

STABLE IN QUINONE FORM

UNAFFECTED BY DIL ACIDS, DESTROYED BY ALKALI HYDROXIDES & REDUCING AGENTS

Phytonadione is stable to heat and moisture and may be autoclaved.

4.2.10 Decomposition
When heated to decomposition it emits acrid smoke and irritating fumes.

4.2.11 pH
SOLN OF 1 PART VIT K1 & 20 PARTS ALC IS NEUTRAL TO LITMUS

4.2.12 Kovats Retention Index
Standard non-polar 3287

4.3 Spectral Properties
Index of refraction: 1.5263 @ 20 deg C/D; specific optical rotation (dioxane): -0.28 @ 589 nm
UV max absorption (petroleum ether): 242, 248, 260, 269, 325 nm (E= 396, 419, 383, 387, 68, 1%, 1 cm)


SADTLER REF NUMBER: 16104 (IR, PRISM)


IR: 5231 (Coblentz Society Spectral Collection)


UV: 2-826 (Organic Electronic Spectral Data, Phillips et al, John Wiley & Sons, NY)


4.3.1 Infrared Spectra

<table>
<thead>
<tr>
<th>Infrared Spectra: 1 of 2 (FTIR Spectra)</th>
</tr>
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<tbody>
<tr>
<td>Instrument Name</td>
</tr>
<tr>
<td>Technique</td>
</tr>
<tr>
<td>Source of Spectrum</td>
</tr>
<tr>
<td>Source of Sample</td>
</tr>
<tr>
<td>Catalog Number</td>
</tr>
<tr>
<td>Lot Number</td>
</tr>
<tr>
<td>Copyright</td>
</tr>
</tbody>
</table>
4.3.2 Mass Spectrometry

4.3.2.1 GC-MS

1. GC-MS Spectrum 2301 - GC-MS
11. GC-MS Spectrum 31506
21. GC-MS Spectrum 31
2. GC-MS Spectrum 2304 - GC-MS (1 TMS)  
3. GC-MS Spectrum 2313 - GC-MS (2 TMS)  
4. GC-MS Spectrum 2318 - GC-MS (2 TMS)  
5. GC-MS Spectrum 2321 - GC-MS (2 TMS)  
6. GC-MS Spectrum 2329 - GC-MS (2 TMS)  
7. GC-MS Spectrum 2332 - GC-MS (2 TMS)  
8. GC-MS Spectrum 11862  
9. GC-MS Spectrum 28236  
10. GC-MS Spectrum 28237  
11. MS-MS Spectrum 89529  
12. GC-MS Spectrum 31507  
13. GC-MS Spectrum 31508  
14. GC-MS Spectrum 31509  
15. GC-MS Spectrum 31510  
16. GC-MS Spectrum 31511  
17. GC-MS Spectrum 31512  
18. GC-MS Spectrum 31587  
19. GC-MS Spectrum 31588  
20. GC-MS Spectrum 31589

from Human Metabolome Database (HMDB)

4.3.2.2 MS-MS

1. MS-MS Spectrum 89529  
2. MS-MS Spectrum 89530  
3. MS-MS Spectrum 89531  
4. MS-MS Spectrum 152475  
5. MS-MS Spectrum 152476  
6. MS-MS Spectrum 152477

from Human Metabolome Database (HMDB)
5 Related Records

CLICK TO LOAD...

5.1 Related Compounds with Annotation

CLICK TO LOAD...

5.2 Related Compounds

<table>
<thead>
<tr>
<th>Description</th>
<th>Records</th>
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</thead>
<tbody>
<tr>
<td>Same Tautomer</td>
<td>25</td>
</tr>
<tr>
<td>Same Connectivity</td>
<td>23</td>
</tr>
<tr>
<td>Same Stereo</td>
<td>5</td>
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<tr>
<td>Same Isotope</td>
<td>13</td>
</tr>
<tr>
<td>Same Parent, Tautomer</td>
<td>30</td>
</tr>
<tr>
<td>Same Parent, Connectivity</td>
<td>28</td>
</tr>
<tr>
<td>Same Parent, Stereo</td>
<td>10</td>
</tr>
<tr>
<td>Same Parent, Isotope</td>
<td>18</td>
</tr>
<tr>
<td>Same Parent, Exact</td>
<td>6</td>
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<tr>
<td>Mixtures, Components, and Neutralized Forms</td>
<td>14</td>
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<tr>
<td>Similar Compounds</td>
<td>4007 records</td>
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<td>-------------------</td>
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<tr>
<td>Similar Conformers</td>
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» from PubChem

### 5.3 Substances

#### 5.3.1 Related Substances

<table>
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<tr>
<th>Type</th>
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<tbody>
<tr>
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<tr>
<td>Same</td>
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<tr>
<td>Mixture</td>
<td>18</td>
</tr>
</tbody>
</table>

» from PubChem

#### 5.3.2 Substances by Category

CLICK TO LOAD...

» from PubChem

### 5.4 Entrez Crosslinks

<table>
<thead>
<tr>
<th>Source</th>
<th>Records</th>
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<tbody>
<tr>
<td>PubMed</td>
<td>1</td>
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<tr>
<td>Protein Structures</td>
<td>1</td>
</tr>
</tbody>
</table>

» from PubChem
6 Chemical Vendors

CLICK TO LOAD...

› from PubChem
7 Drug and Medication Information

7.1 Drug Indication

For the treatment of haemorrhagic conditions in infants, antidote for coumarin anticoagulants in hypoprothrombinaemia.

7.2 FDA Orange Book

7.2.1 Prescription Drug Products

<table>
<thead>
<tr>
<th>Prescription Drug Products: 1 of 9 (RX Drug Ingredient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Ingredient</td>
</tr>
<tr>
<td>Proprietary Name</td>
</tr>
<tr>
<td>Applicant</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

7.2.2 Discontinued Drug Products

<table>
<thead>
<tr>
<th>Discontinued Drug Products: 1 of 5 (DISCN Drug Ingredient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Ingredient</td>
</tr>
</tbody>
</table>
Discontinued Drug Products: 1 of 5 (DISCN Drug Ingredient)

<table>
<thead>
<tr>
<th>Drug Ingredient</th>
<th>FOLIC ACID; NIACINAMIDE; PANTOTHENIC ACID; PHYTONADIONE; PYRIDOXINE; RIBOFLAVIN; THIAMINE; VITAMIN A PALMITATE; VITAMIN E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name</td>
<td>VITAPED</td>
</tr>
<tr>
<td>Applicant</td>
<td>HOSPIRA (Application Number: N020176)</td>
</tr>
</tbody>
</table>

from FDA Orange Book

Discontinued Drug Products: 2 of 5 (DISCN Drug Ingredient)

<table>
<thead>
<tr>
<th>Drug Ingredient</th>
<th>PHYTONADIONE</th>
</tr>
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<tbody>
<tr>
<td>Proprietary Name</td>
<td>PHYTONADIONE</td>
</tr>
<tr>
<td>Applicant</td>
<td>GLAXOSMITHKLINE (Application Number: A084060)</td>
</tr>
</tbody>
</table>

from FDA Orange Book

Discontinued Drug Products: 3 of 5 (DISCN Drug Ingredient)

<table>
<thead>
<tr>
<th>Drug Ingredient</th>
<th>PHYTONADIONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name</td>
<td>VITAMIN K1</td>
</tr>
<tr>
<td>Applicant</td>
<td>HOSPIRA (Application Number: A087956)</td>
</tr>
</tbody>
</table>

from FDA Orange Book

View All 5 Discontinued Drug Products

7.3 Drug Labels for Ingredients

Drug Labels for Ingredients: 1 of 6 (Label Title)

<table>
<thead>
<tr>
<th>Label Information</th>
<th>Total 34 labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Ingredient</td>
<td>PHYTONADIONE</td>
</tr>
<tr>
<td>NDC Code(s)</td>
<td>NDC Code(s) 00005-4365-56, 0179-0133-70, 0187-1704-05, 0409-9157-01, 0409-9157-25, 0409-9158-01, 0409-9158-25, 11695-4014-1, 21695-168-10, 46066-915-01 ... total 55.</td>
</tr>
<tr>
<td>Packagers</td>
<td>Aspen Veterinary Resources; Avera McKennan Hospital; Bimeda Inc., Division of Cross Vetpharm Group; Butler Animal Health; Cardinal Health; Carilion Materials Management; General Injectables &amp; Vaccines, Inc; Hospira, Inc.; International Medication Systems, Limited; KAISER FOUNDATION HOSPITALS; Neogen Corporation - Nandino; Physicians Total Care, Inc.; Rebel Distributors Corp; Sandoz Canada Inc; Teligent Pharma, Inc.; Ultimate Formulations Inc. dba Best Formulations; Valeant Pharmaceuticals North America LLC;</td>
</tr>
</tbody>
</table>
### Drug Labels for Ingredients: 1 of 6 (Label Title)

Wyeth Pharmaceutical Division of Wyeth Holdings LLC, a subsidiary of Pfizer Inc.

› from DailyMed

### Drug Labels for Ingredients: 2 of 6 (Label Title)

<table>
<thead>
<tr>
<th>Label Information</th>
<th>Total 143 labels</th>
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</thead>
<tbody>
<tr>
<td>Drug Ingredient</td>
<td>VITAMIN K</td>
</tr>
<tr>
<td>NDC Code(s)</td>
<td>NDC Code(s)</td>
</tr>
<tr>
<td>Packagers</td>
<td>A-S Medication Solutions; Aidarex Pharmaceuticals LLC; American Health Packaging; Amneal Pharmaceuticals LLC; Aphena Pharma Solutions - Tennessee, Inc.; Aphena Pharma Solutions - Tennessee, LLC; Aspen Veterinary Resources; Avera McKennan Hospital; Bimeda Inc., Division of Cross Vetpharm Group; Bristol-Myers Squibb Pharma Company ... total 53.</td>
</tr>
</tbody>
</table>

› from DailyMed

### Drug Labels for Ingredients: 3 of 6 (Label Title)

#### Label Title

INFUVITE ADULT MULTIPLE VITAMINS- ascorbic acid, vitamin a palmitate, cholecalciferol, thiamine hydrochloride, riboflavin-5 phosphate sodium, pyridoxine hydrochloride, niacinamide, dextranthenol, alpha-tocopherol acetate, vitamin k1, folic acid, biotin, cyanocobalamin injection, solution

More information...

#### Drug Ingredient

**ALPHA-TOCOPHEROL ACETATE**; **ASCORBIC ACID**; **BIOTIN**; **CHOLECALCIFEROL**; **CYANOCOBALAMIN**; **DEXPANTHENOL**; **FOLIC ACID**; **NIACINAMIDE**; **PYRIDOXINE HYDROCHLORIDE**; **RIBOFLAVIN 5'-PHOSPHATE SODIUM**; **THIAMINE HYDROCHLORIDE**; **VITAMIN A PALMITATE**; **VITAMIN K**

#### Label Image

CLICK TO LOAD...

#### Label Download

PDF Label
### Drug Labels for Ingredients: 3 of 6 (Label Title)

<table>
<thead>
<tr>
<th>NDC Code(s)</th>
<th>Packager</th>
</tr>
</thead>
<tbody>
<tr>
<td>54643-5649-1, 54643-5650-2</td>
<td>Sandoz Canada Inc</td>
</tr>
</tbody>
</table>

View All 6 Drug Labels for Ingredients

### 7.4 Drugs at PubMed Health

#### Drugs at PubMed Health: 1 of 7 (PubMed Health Drug Name)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K (Class) (Oral route, Parenteral route)</td>
<td>Vitamins are compounds that you must have for growth and health. They are needed in only small amounts and usually are available in the foods that you eat. Vitamin K is necessary for normal clotting of the blood.</td>
</tr>
</tbody>
</table>

**from PubMed Health**

#### Drugs at PubMed Health: 2 of 7 (PubMed Health Drug Name)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mephyton</td>
<td>See Phytonadione</td>
</tr>
</tbody>
</table>

**from PubMed Health**

#### Drugs at PubMed Health: 3 of 7 (PubMed Health Drug Name)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytonadione</td>
<td>Antidote, Nutriceutical, Nutritive Agent</td>
</tr>
</tbody>
</table>

**from PubMed Health**

View All 7 Drugs at PubMed Health

### 7.5 Clinical Trials

#### 1 to 5 of 21 View More

<table>
<thead>
<tr>
<th>Record ID</th>
<th>Title</th>
<th>Status</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03358706</td>
<td>A Study to Evaluate the Effect of [Ustekinumab](<a href="https://pubchem.ncbi.nlm.nih.gov/compound/Phylloquinone#secti">https://pubchem.ncbi.nlm.nih.gov/compound/Phylloquinone#secti</a>...</td>
<td>Not yet recruiting</td>
<td>1</td>
</tr>
</tbody>
</table>
### ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Record ID</th>
<th>Title</th>
<th>Status</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02740712</td>
<td>Pharmacokinetic Drug-Drug Interaction Study of Rucaparib</td>
<td>Active, not recruiting</td>
<td>1</td>
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<tr>
<td>NCT02324686</td>
<td>Vitamin K Supplementation in Patients on Hemodialysis</td>
<td>Recruiting</td>
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</tr>
<tr>
<td>NCT02256813</td>
<td>Study to Evaluate the Effect of Multiple Doses of BIRT 2584 XX Tablets on the Pharmacokinetic Parameters of Warfarin, Omeprazole, Caffeine, and Dextromethorphan in Healthy Male Volunteers</td>
<td>Completed</td>
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<tr>
<td>NCT02243553</td>
<td>Effects of Tipranavir (With Ritonavir) Capsule and Liquid Formulation on Cytochrome P450 and P-glycoprotein Activity in Healthy Volunteers</td>
<td>Completed</td>
<td>1</td>
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</tbody>
</table>

### 7.6 Therapeutic Uses

**Antifibrinolytic Agents**

*National Library of Medicine's Medical Subject Headings online file (MeSH, 1999)*

**Vitamin K**

The rational therapeutic use of vitamin K is based on its ability to correct bleeding tendency or hemorrhage assoc with its deficiency. A deficiency of vitamin K & its attendant deficiency of prothrombin & related clotting factors can result from inadequate intake, absorption, or utilization of vitamin, or as a consequence of action of the action of a vitamin K antagonist. /Vitamin K/


**Bleeding** that accompanies obstructive jaundice or biliary fistula responds promptly to administration of vitamin K. Oral phytonadione admin with bile salts is both safe and effective and should be used in the care of the jaundiced patient, both preoperatively & postoperatively.


**If** for some reason oral admin is not feasible /in treatment of obstructive jaundice or biliary fistula/, a parenteral prep should be used.


**Vit K** may be of help in combating bleeding and hypoprothrombinemia that follow the bite of the tropical American pit viper or other species whose venom destroys or inactivates prothrombin. /Vitamin K/


MEDICATION (VET): PARENTERAL THERAPY IS INDICATED IN SWEET CLOVER DISEASES & POSSIBLY IN SOME MYCOTOXICOSES & HEMATURIAS OF CATTLE. ... IT MAY HAVE VALUE IN PROPHYLAXIC AS WELL AS IN TREATMENT OF EPISTAXIS IN RACE HORSES. FED TO SOWS IT HELPS PREVENT HEMORRHAGING NAVELS IN NEW BORN PIGS... /VIT K/

MEDICATION (VET): TO PREVENT & TREAT BLOOD COAGULATION PROBLEMS (HEMORRHAGIC SYNDROME) ASSOC WITH HYPOPROTHROMBINEMIA. IT IS REQUIRED FOR LIVER PROTHROMBIN SYNTHESIS. ... PRESURGICAL USE OF VIT K IS ESSENTIAL IN ANIMALS WITH INADEQUATE SECRETION OF BILE & IN NEWBORN (LITTLE OR NO INTESTINAL BACTERIAL SYNTHESIS OF VIT K). /VIT K/

MEDICATION (VET): IN HYPOPROTHROMBINEMIAS; ANTIDOTE FOR DICOUMAROL POISONING

Vitamin K is indicated for treatment and prevention of various coagulation disorders involving impaired formation of factors II, VII, IX, and X resulting from vitamin K deficiency or impairment of vitamin K activity, including hypoprothrombinemia due to oral anticoagulants, salicylates, and some antibiotics. vitamin K does not return abnormal platelet function to normal. Vitamin K does not counteract the anticoagulant activity of heparin. Vitamin K may not be effective in hepatic function impairment since prothrombin synthesis occurs in the liver. /Vitamin K; Included in US product labeling/

The American Academy of Pediatrics recommends routine phytonadione administration at birth to prevent hemorrhagic disease of the newborn, since vitamin K from the mother may be inadequate because of poor passage through the placenta and because intestinal bacteria responsible for natural synthesis of vitamin K are not present for 5 to 8 days following birth. in addition, the risk of hemorrhagic disease of the newborn is increased in infants of mothers who received anticonvulsants (eg, phenobarbital, phenytoin) during pregnancy. Phytonadione is preferred over menadiol because the risk of causing hyperbilirubinemia and hemolytic anemia is less, especially in premature infants. /Vitamin K;
Phytonadione is useful in restoring the prothrombin time to normal levels and in decreasing or stopping bleeding episodes.


Phytonadione and other Vitamin K preparations do not combat hemorrhage caused by overdosage of heparin.


Phytonadione has a more prompt, potent, and prolonged effect than the other vitamin K analogues and is generally preferred when large doses or long-term therapy is indicated....


Anticoagulants are indicated for prophylaxis and/or treatment of venous (or arterial) thrombosis (and its extension) and pulmonary embolism. Deep vein thrombosis (DVT) or pulmonary embolism (treatment). Oral anticoagulants are used during and following initial heparin therapy to decrease the risk of extension, recurrence, or death. /Anticoagulants; Included in US product labeling/


Oral anticoagulants are used to prevent thromboembolic complications after surgery, although low-dose subcutaneous heparin is used more commonly. [Anticoagulants; Included in US product labeling/}


Anticoagulants are indicated for prophylaxis and/or treatment of thromboembolic complications (ischemic stroke) associated with atrial fibrillation. They are strongly recommended in patients at high risk of stroke (including patients with recent stroke, transient ischemic attack, or systemic embolism; poor left ventricular function; age over 75 years; hypertension; rheumatic mitral valve disease; mechanical or tissue prosthetic heart valves.) [Anticoagulants; Included in US product labeling/}


Anticoagulants are indicated after myocardial infarction to reduce the risk of death, recurrent
myocardial infarction, and thromboembolic events such as stroke or systemic embolization.

Anticoagulants; Included on U.S. product labeling/


Oral anticoagulants are indicated, alone or in combination with aspirin, for primary prevention of thrombotic complications of coronary artery disease in patients without history of myocardial infarction, stroke, or transient ischemic attacks but with increasing levels of risk. /Anticoagulants, Included in US product labeling/


Anticoagulants are indicated for prophylaxis and/or treatment of thromboembolic complications associated with tissue and mechanical cardiac valve replacement. /Anticoagulants; Included in US product labeling/


Anticoagulants are used in certain patients with valvular heart disease to prevent systemic embolization. /NOT included in US product labeling/


Anticoagulants are used, following initial heparinization, to prevent recurrent thromboembolism in peripheral arterial occlusive disease. They are not indicated for routine prophylaxis after intrainguinal bypass and other vascular reconstructions but are indicated, usually in combination with aspirin, in patients at high risk of graft thrombosis. /NOT included in US product labeling/


7.7 Drug Warning

IN PT WHO HAVE SEVERE HEPATIC DISEASE, ADMIN OF LARGE DOSES OF MENADIONE OR PHYLLOQUINONE MAY FURTHER DEPRESS FUNCTION OF LIVER.


Maternal Medication usually Compatible with Breast-Feeding: K1 (vitamin): Reported Sign or Symptom in Infant or Effect on Lactation: None. /from Table 6/

A rare hypersensitivity-like reaction, which has occasionally resulted in death, has been reported after intravenous administration of phytonadione, especially when administration is rapid.

**Phytonadione** is relatively nontoxic; however, severe reactions have occurred rarely during or immediately following IV administration. These severe reactions, which may occur in patients receiving phytonadione for the first time, resemble hypersensitivity or anaphylaxis. Symptoms include cramp-like pains, convulsive movements, cardiac irregularities, chest pains, cyanosis, dulled consciousness, flushing of the face, a sense of chest constriction, circulatory collapse, bronchospasm, hyperhidrosis, dyspnea, alteration of taste, dizziness, rapid and weak pulse, brief hypotension, shock, cardiac and/or respiratory arrest, and death.

Spontaneous abortion and stillbirth have occurred, as well as low birth weight and growth retardation. In addition, fetal or neonatal hemorrhage, fetal death from hemorrhage in utero, and increased risk of maternal hemorrhage during the second and third trimesters have been reported. There is some evidence that embryopathy occurs only with oral anticoagulant administration between the 6th and 12th weeks of gestation. If a coumarin or indandione derivative is used during the third trimester, it should be discontinued after the 37th week of gestation, and heparin substituted if maternal anticoagulation is required, to reduce the risk of fetal hemorrhage during labor and of neonatal hemorrhage following delivery. Anticoagulants also increase the risk of maternal hemorrhage during or following delivery.

In newborns, especially premature infants, mendiol sodium diphosphate has been associated with hemolytic anemia, hyperbilirubinemia, and kernicterus because of immature hepatic function in these infants. There is less risk with phytonadione, unless high doses are given.

Side/Adverse Effects: Flushing of face; redness, pain, or swelling at injection site (with parenteral administration); skin lesions (plaques) -- very rare, with repeated injection at one site; unusual taste.

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Administration of anticoagulants in the immediate postpartum period may increase the risk of maternal hemorrhage. [Anticoagulants/]

Infants, especially neonates, may be more susceptible to the effects of anticoagulants because of vitamin K deficiency. [Anticoagulants/]

Geriatric patients may be more susceptible to the effects of anticoagulants, increasing the risk of hemorrhage. Geriatric patients may have advanced vascular disease that alters hemostatic mechanisms, hepatic function impairment that decreases procoagulant factor synthesis or anticoagulant metabolism, or they may have renal function impairment. Lower maintenance doses than those usually recommended for adults may be required for these patients. [Anticoagulants/]

Anticoagulant therapy increases the risk of localized hemorrhage during and following oral surgical procedures. Consultation with the prescribing physician may be advisable prior to oral surgery, to determine whether a temporary dosage reduction or withdrawal of anticoagulant therapy is feasible. Also, local measures to minimize bleeding should be used at the time of surgery. [Anticoagulants/]

The occurrence of gastrointestinal or genitourinary hemorrhage during anticoagulant therapy, especially if the prothrombin time is within the therapeutic range, may indicate the presence of an underlying occult lesion such as a tumor or ulcer. [Anticoagulants/]

Necrosis is caused by thrombosis of the venules and capillaries within the subcutaneous fat. It usually occurs on the 3rd to 8th day of therapy and may be more frequent in patients with protein C deficiency. Initial lesions, which are painful, are erythematous or ecchymotic with a sharply demarcated border, subsequently developing bullae with full-thickness skin necrosis. It is important to determine whether necrosis is caused by the anticoagulant or by an underlying disease. In severe cases, debridement or even amputation of affected tissue, limb, breast, or penis may be necessary. Fatalities have occurred. [Anticoagulants/]

VITAMIN K1 | C31H46O2 - PubChem
https://pubchem.ncbi.nlm.nih.gov/compound/Phylloquinone#section
Constipation may be a symptom of hemorrhage-induced paralytic ileus or intestinal obstruction caused by submucosal or intramural hemorrhage. /Anticoagulants/  

Fatal or nonfatal bleeding or hemorrhage can occur from any tissue or organ. Signs, symptoms, and severity vary depending on the site and extent of bleeding. Therefore, bleeding should be considered as a potential cause of any sign or symptom not otherwise explainable. /Anticoagulants/  

Purple toes syndrome may develop 3 to 20 weeks after initiation of anticoagulant therapy; it results from systemic cholesterol microembolization. Anticoagulant therapy may enhance the release of atheromatous plaque emboli, which may increase the risk of purple toes syndrome and other complications of systemic cholesterol embolization. Purple spots may blanch with pressure or elevation on the leg. The syndrome is usually reversible but in some cases may progress to gangrene or necrosis. /Anticoagulants/  

Adrenal hemorrhage may result in acute adrenal insufficiency. Diagnosis may be difficult because the initial symptoms (abdominal pain, apprehension, diarrhea, dizziness or fainting, headache, loss of appetite, nausea or vomiting, and weakness) are nonspecific and variable. /Anticoagulants/  

Large amounts of aluminum hydroxide may precipitate bile acids in the upper small intestine, thereby decreasing absorption of fat-soluble vitamins. /Vitamin K/  

Concurrent use /with cholestyramine, colestipol, mineral oil, or sucralfate/ may decrease absorption of vitamin K; requirements for vitamin K may be increased in patients receiving these medications. /Vitamin K/  

Oral and intramuscular phytomenadione (vitamin K1) prophylaxis became an issue following the report of a potential carcinogenic effect of intramuscular but not oral phytomenadione prophylaxis. There is
increasing evidence, however, that oral phytomenadione prophylaxis is less effective for the prevention of late vitamin K deficiency bleeding (VKDB) than intramuscular prophylaxis. Following a report of an increased cancer risk after intramuscular phytomenadione, a series of papers on this issue appeared. Although an increased risk for solid tumours could almost certainly be excluded, a potential risk for acute lymphatic leukaemia in childhood could not be ruled out definitively. Almost all cases of late VKDB are preventable with intramuscular phytomenadione prophylaxis administered once at birth, whereas a single oral dose given at birth is much less effective. Repeated oral phytomenadione doses given to breast-fed infants either weekly (1 mg) or daily (25 microg) seem to be as effective as intramuscular phytomenadione prophylaxis. The efficacy of 3 oral 2mg doses with the new mixed micellar preparation ("Konakion MM") remains to be established. Although a number of studies have failed to confirm a cancer risk with phytomenadione, these studies have been unable to rule out a risk definitely because absence of evidence is not evidence of absence. A meta-analysis of the available studies might provide 95% confidence intervals narrow enough to exclude even a small cancer risk with some certainty. Oral prophylaxis will probably be as safe as the intramuscular prophylaxis if given daily (25 microg) or weekly (1 mg).


7.8 Drug Tolerance

HEREDITARY RESISTANT INDIVIDUALS TO COUMARIN WERE FOUND TO SHOW ANOTHER CHARACTERISTIC, UNUSUAL SENSITIVITY TO ANTIDOTAL EFFECTS OF VIT K. ... SENSITIVITY WAS...CALCULATED TO BE ABOUT 20 TIMES THAT OBSERVED IN OTHER PATIENTS. ...SYNTHESIS OF CLOTTING FACTOR II, VII, IX & X HAS BEEN MODIFIED BY GENETIC MUTATION... /VIT K/

8 Pharmacology and Biochemistry

8.1 Pharmacology

Phylloquinone is a vitamin, indicated in the treatment of coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity. Phylloquinone aqueous colloidal solution of vitamin K1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X).

› from DrugBank

8.2 MeSH Pharmacological Classification

Vitamins

Organic substances that are required in small amounts for maintenance and growth, but which cannot be manufactured by the human body.

See a list of PubChem compounds matching this category.

› from MeSH

Antifibrinolytic Agents

Agents that prevent fibrinolysis or lysis of a blood clot or thrombus. Several endogenous antiplasmins are known. The drugs are used to control massive hemorrhage and in other coagulation disorders.

See a list of PubChem compounds matching this category.

› from MeSH

8.3 ATC Code

B02BA01 - Phytomenadione < B02BA - Vitamin k < B02B - Vitamin k and other hemostatics < B02 - Antihemorrhagics < B - Blood and blood forming organs

› from WHO ATC

8.4 Bionecessity

The discovery of a vitamin K dependent protein in bone suggests that the fetal bone abnormalities associated with the administration of oral anticoagulants during the first trimester of pregnancy "fetal warfarin syndrome" may be related to a deficiency of the vitamin. /Vitamin K/


› from HSDB

State of deficiency: chief clinical manifestation of vitamin k deficiency is increased tendency to bleed, and postoperative hemorrhage are common; intracranial hemorrhage may occur. /vit k/

Hypoprothrombinemia secondary to vitamin K deficiency may occur in the following persons or conditions: Patients with hepatic or biliary tract disease, including obstructive jaundice or biliary fistula; in malabsorption syndromes or diseases affecting the small intestine or pancreas, such as celiac disease, cystic fibrosis, intestinal resuction, persistent diarrhea or dysentercy, regional enteritis, sprue, or ulcerative colitis; prolonged T-tube drainage; abetalipoproteinemia; patients receiving total parenteral nutrition (TPN); or in infants receiving unfortified milk substitute formulas or those who are exclusively breast-fed. Also vitamin K deficiency may occur when vitamin K activity is impaired by sulfonamides, quinine, quinidine, or dactinomycin, or when absorption is decreased by concurrent administration of cholestyramine, colestipol, mineral oil, or sucralfate. /Vitamin K/

8.5 Absorption, Distribution and Excretion

Oral phylloquinone is adequately absorbed from the gastrointestinal tract only if bile salts are present. After absorption, phylloquinone is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues.

Route of Elimination

Almost no free unmetabolized vitamin K appears in bile or urine.

Little is known about the excretion of vitamin K. High fecal concentrations of vitamin K probably result from bacterial synthesis in the intestine.

Although the drug may be concentrated in the liver for a short time after absorption, only small amounts of phytonadione are stored in body tissues.

Phytonadione is absorbed from the GI tract only in the presence of bile salts. Radioisotope studies show that absorption occurs via intestinal lymph. There is some evidence that absorption of phytonadione across the GI mucosa is a saturable, energy-dependent process that occurs in the proximal small intestine.

Fat-soluble vit...k...absorbed from skin... /vit k/

Vitamin K accumulates in liver, spleen, and lungs, but significant amounts are not stored in body for long periods.


Phytonadione is absorbed rapidly by the subcutaneous route. The subcutaneous route is preferable to the intravenous route unless problems are anticipated with subcutaneous absorption.


Phylloquinone is absorbed chemically unchanged from the proximal intestine after solubilization into mixed micelles composed of bile salts and the products of pancreatic lipolysis. In healthy adults, the efficiency of absorption of phylloquinone in its free form is about 80%, but the efficiency of absorption from green leafy vegetables such as spinach is < 10%.


8.6 Metabolism/Metabolites

...In experimental animals...phylloquinone...can be converted to more potent menaquinone series. Whether this can occur in man and of what significance these transformations are to action of phylloquinone...are still unknown.


In animals treated with warfarin, major fraction of phylloquinone is metabolized to phylloquinone oxide.


Phytonadione is rapidly metabolized to more polar metabolites, which are excreted in the bile and urine. The major urinary metabolites result from shortening of the side chain to five or seven carbon atoms, yielding carboxylic acids that are conjugated with glucuronate prior to excretion. Treatment with a coumarin-type anticoagulant results in a marked increase in the amount of phytonadione-2,3-epoxide in the liver and blood. Such treatment also increases the urinary excretion of phytonadione metabolites, primarily degradative products of phytonadione-2,3-epoxide. The biliary metabolites of phytonadione have not been identified.


The liver plays an exclusive role in the metabolic transformations leading to the elimination of vitamin K from the body. After intravenous doses of 45 ug to 1 mg (3)H-phylloquinone, about 20% of the radiolabel was excreted in the urine within three days, and 35-50% was excreted as metabolites in the feces via the bile.
8.7 Mechanism of Action

Vitamin K is an essential cofactor for the gamma-carboxylase enzymes which catalyze the posttranslational gamma-carboxylation of glutamic acid residues in inactive hepatic precursors of coagulation factors II (prothrombin), VII, IX and X. Gamma-carboxylation converts these inactive precursors into active coagulation factors which are secreted by hepatocytes into the blood. Supplementing with Phylloquinone results in a relief of vitamin K deficiency symptoms which include easy bruisability, epistaxis, gastrointestinal bleeding, menorrhagia and hematuria.

8.8 Human Metabolite Information

8.8.1 Metabolite Description

Vitamin K is a family of fat-soluble compounds with a common chemical structure based on 2-methyl-1,
Phytonadione is often called vitamin K1. It is a fat-soluble vitamin that is stable to air and moisture but decomposes in sunlight. It is found naturally in a wide variety of green plants. Phyloquinone is also an antidote for coumatetralyl. Vitamin K is needed for the posttranslational modification of certain proteins, mostly required for blood coagulation.

8.8.2 Biofluid Locations

1. Blood
2. Urine

8.8.3 Cellular Locations

1. Extracellular
2. Membrane (predicted from logP)

8.8.4 Metabolite Pathways

1. Acenocoumarol Pathway
2. Alteplase Pathway
3. Aminocaproic Acid Pathway
4. Anistreplase Pathway
5. Aprotinin Pathway
6. Ardeparin Pathway
7. Argatroban Pathway
8. Bivalirudin Pathway
9. Coagulation
10. Dicoumarol Action Pathway
11. Dicumarol Pathway
12. Enoxaparin Pathway
13. Fondaparinux Pathway
14. Heparin Pathway
15. Lepirudin Pathway
16. Phenindione Action Pathway
17. Phenprocoumon Pathway
18. Reteplase Pathway
19. Streptokinase Pathway
20. Tenecteplase Pathway
21. Tranexamic Acid Pathway
22. Urokinase Pathway
23. Vitamin K Metabolism
24. Warfarin Pathway
25. Ximelagatran Pathway
9 Use and Manufacturing

9.1 Methods of Manufacturing

Partial syntheses from menadione and phytol ... Synthesis using a pi-allylic nickel(I) complex ... .


Synthetically from 2-methyl-1,4-naphthoquinone and phytol.


The first syntheses and structural elucidation of phylloquinone were published in 1939 almost simultaneously by four groups. The starting materials were menadione or menadiol as the aromatic component and natural phytol or one of its derivatives. A breakthrough in commercial synthesis was achieved in the 1950s, when it was found that monoacylated menadiols (e.g. the monoacetate or the monobenzoate) could be used advantageously in the alkylation step and that natural phytol could be replaced by isophytol, which is easy to synthesize.


9.2 Impurities

Commercial preparations may contain up to 20% of the cis isomer.


Commercially available phylloquinone (vitamin K1) is prepared synthetically and may contain not only 2',3'-trans-phylloquinone (not less than 75%), but also 2',3'-cis-phylloquinone and trans-epoxyphylloquinone (not more than 4.0 percent). Phylloquinone occurs in nature only as the 2',3'-trans-7R,11R-stereoisomer.


9.3 Formulations/Preparations

PHYTONADIONE, USP (VIT K1, AQUAMEPHYTON, KONAKION, MEPHYTON)... MARKETED IN 5-MG TABLETS, & IN AMPULS CONTAINING EMULSION OF 2 OR 10 MG/ML OF PHYTONADIONE DISPERSED IN SOLN OF BUFFERED POLYSORBATE & PROPYLENE GLYCOL (KONAKION) OR POLYETHYLATED FATTY ACID DERIV & DEXTROSE (AQUAMEPHYTON).

KONAKION IS ADMIN ONLY IM; AQUAMEPHYTON MAY BE GIVEN BY ANY PARENTERAL ROUTE.


COLLOIDAL SOLN IS MARKETED UNDER NAME AQUA-MEPHYTON.


Oral tablets; 5 mg, Mephyton (scored) Merck.


Phylloquinone is available as a 5 and 10 mg tablet (chewable), a 2 and 10 mg/mL injection solution, a 10 and 20 mg/mL oral solution, and a 20 mg/mL emulsion. ... Phylloquinone is also available as a component (200 ug) of a multivitamin lyophilized, sterile powder intended for reconstitution and dilution in intravenous infusions, as a component (0.075 mg) of and effervescent multivitamin tablet, and as a component (5.5 ug) of a multivitamin infant formula.


Parenteral injection; 2 mg/ml, AquaMEPHYTON (with polyoxyethylated fatty acid derivative, dextrone, and benzyl alcohol 0.9%), Merck. 10 mg/ml, AquaMEPHYTON (with polyoxyethylated fatty acid derivative, dextrose, and benzyl alcohol 0.9%), Merck.

10 Identification

10.1 Analytic Laboratory Methods

Several international pharmacopoeias specify infrared (IR) and ultraviolet (UV) absorption spectrophotometry with comparison to standards as the methods to identify phylloquinone; UV absorption spectrophotometry and liquid chromatography are used to assay its purity. Phylloquinone is identified in pharmaceutical preparations by IR and UV absorption spectrophotometry and liquid chromatography; liquid chromatography is used to assay for its content.


AOAC International (1996) has developed a liquid chromatographic method with UV detection for the determination of phylloquinone in ready-to-feed milk-based infant formula.


AOAC Official Method 992.27: trans-Vitamin K1 (phylloquinone) in ready-to-feed milk-based infant formula; liquid chromatographic method.


10.2 Clinical Laboratory Methods

QUANTITATIVE ANALYSIS OF VITAMIN K1 & VITAMIN K1 2,3-EPOXIDE IN PLASMA BY ELECTRON-CAPTURE GAS-LIQUID CHROMATOGRAPHY.

BECHTOLD H, JAENCHEN E; QUANTITATIVE ANALYSIS OF VITAMIN K1 & VITAMIN K1 2,3-EPOXIDE IN PLASMA BY ELECTRON-CAPTURE GAS-LIQUID CHROMATOGRAPHY; J CHROMATOGR 164(1) 85-90 (1979)

As a result of its high selectivity and sensitivity, high-performance liquid chromatography (HPLC) is the method of choice for the determination of phylloquinone and menaquinones in the blood, tissues, milk, and in foods. Various procedures for extraction and preliminary purification, normal or reversed-phase HPLC, and ultraviolet, electrochemical, and fluorescence detection (both after electrochemical or chemical reduction and after photochemical decomposition) of the vitamin K substances have been described. The detection limits for phylloquinone are in the range 25-500 pg, depending on the detection method used. ... Alternative methods are thin layer chromatography, high-performance thin layer chromatography and gas chromatography. The spectrophotometric, fluorimetric, and colorimetric methods previously used without chromatographic purification of the samples to be analysed are frequently less sensitive and less specific than HPLC, for instance allowing no distinction between phylloquinone and menaquinones.

11 Safety and Hazards

11.1 Hazards Identification

11.1.1 GHS Classification

**GHS Hazard Statements**
Aggregated GHS information provided by 42 companies from 3 notifications to the ECHA C&L Inventory.

Reported as not meeting GHS hazard criteria by 14 of 42 companies. For more detailed information, please visit ECHA C&L website

Of the 2 notification(s) provided by 28 of 42 companies with hazard statement code(s):

H413 (96.43%): May cause long lasting harmful effects to aquatic life [Hazardous to the aquatic environment, long-term hazard]

Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.

**Precautionary Statement Codes**
P273, and P501
(The corresponding statement to each P-code can be found [here](#)).

from European Chemicals Agency - ECHA

11.2 Accidental Release Measures

11.2.1 Disposal Methods

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices.

from HSDB

11.3 Handling and Storage

11.3.1 Storage Conditions

KEEP WELL CLOSED & PROTECTED FROM LIGHT.

The drug is photosensitive and must be protected from light at all times. Infusion solutions should be protected from light by wrapping the container with aluminum foil or other opaque material. Phytonadione tablets should be stored in well-closed, light-resistant containers.
11.4 Regulatory Information

11.4.1 FDA Requirements

The US Food and Drug Administration ... requires that all infant formula sold in the USA contain a minimum of 4 ug/100 kcal (0.2 mg/kg) of vitamin K; and that any vitamin K added shall be in the form of phylloquinone.


The Approved Drug Products with Therapeutic Equivalence Evaluations List identifies currently marketed prescription drug products, incl phytonadione, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act.

12 Toxicity

12.1 Toxicological Information

12.1.1 Carcinogen

Evaluation: There is inadequate evidence in humans for the carcinogenicity of vitamin K. There is inadequate evidence in experimental animals for the carcinogenicity of vitamin K. Overall evaluation: Vitamin K is not classifiable as to its carcinogenicity to humans (Group 3). 


12.1.2 Interactions

Vit k antagonizes inhibitory effect of /acenocoumarol, phenprocoumon, anisindione, diphenadione, & phenindione/ on hepatic synthesis of vit k-dependent clotting proteins...


Requirements for vitamin K may be increased in patients receiving /broad-spectrum antibiotics, moxalactam, quinidine, quinine, high doses of salicylates, or antibacterial sulfonamides/.


Concurrent use /with dactinomycin/ may decrease the effects of vitamin K; evidence is inconclusive, observation of patients is recommended and a higher dose of vitamin K may be required. 


Concurrent use /of coumarin- or indandione-derivative anticoagulants/ with vitamin K may decrease the effects of these anticoagulants as a result of increased hepatic synthesis of procoagulant factors. When reinstituting oral anticoagulant therapy after the administration of large doses of vitamin K, it may be necessary to temporarily increase the dose of the oral anticoagulant, or to use one such as heparin that acts on a different principle. 


Effects of anticoagulants may be increased paradoxically because of decreased hepatic synthesis of procoagulant factors; this effect may depend on antithyroid dosage and subsequent thyroid status of the patient. 

/Anticoagulants/
Effects of anticoagulants may be decreased because of increased hepatic synthesis of procoagulant factors by estrogens; however, increased effects have also been reported. Use of estrogen-containing oral contraceptives in patients with thrombophilic disorders tends to increase the risk of thrombosis, especially in patients with activated protein C resistance due to factor V Leiden mutation.

The effects of anticoagulants may be increased if used concurrently with difunisal, possibly in part because of displacement of anticoagulant from protein binding sites.

Effects of anticoagulants may be increased if used concurrently with cinchophen, possibly because of alteration of procoagulant factor synthesis or catabolism or displacement of anticoagulant from protein binding sites.

Effects of anticoagulants may be increased when used concurrently with clofibrate, possibly because of alteration of procoagulant factor synthesis or catabolism or displacement of anticoagulant from protein binding sites.

Effects of anticoagulants may be decreased when use concurrently with glutethimide because of accelerated metabolism of anticoagulant secondary to stimulation of hepatic microsomal enzyme activity.

Effects of anticoagulants may be increased when used concurrently with lepirudin; gradual reduction in dose and/or infusion rate of lepirudin is recommended prior to switching to an oral anticoagulant.

Inhibition of the cytochrome p450 enzyme system by omeprazole especially in high doses, may cause a
decrease in hepatic metabolism of anticoagulants, which may result in delayed elimination and increased blood concentration. 

A pharmacodynamic interaction may occur that causes an increased bleeding diathesis despite unaltered PT; since there is little clinical experience, caution is advised when these agents (paroxetine and anticoagulants) are used concurrently.

Effects of anticoagulants may be increased when used concurrently with platelet aggregation inhibitors; the effect will not be reflected in PT.

Effects of anticoagulants may be increased because of plicamycin’s hypoprothrombinemic effect. Interference with platelet formation by plicamycin may result in increased risk of hemorrhage; this effect cannot be shown by measurement of PT.

Effects of anticoagulants may be increased when used concurrently with thyroid hormones because of alteration of procoagulant factor synthesis or catabolism and increased receptor affinity for anticoagulant; this effect may depend upon dosage and subsequent thyroid status of the patient.

Caution in concurrent use of sertraline with anticoagulants is recommended because of possible displacement of either medication from protein-binding sites, leading to increased plasma concentrations of the free (unbound) medications and increased risk of adverse effects.

The pharmacological response to vitamin K1 (Konakion) in anticoagulated (prothrombin complex activity <30%) New Zealand white rabbits was determined by measuring prothrombin complex activity (P.C.A.) in peripheral plasma. In animals pretreated with difenacoum (0.85 mg/kg or 8.5 mg/kg) P.C.A. reached a max 4 hr after admin of vitamin K1 (0.5 mg/kg) and declined at a rate indicating complete inhibition of clotting factor synthesis. The duration of action of difenacoum was much longer than that of
warfarin. ... Difenacoum /is a/... more potent and persistent antagonist of vitamin K1 than warfarin in vivo. ...

Abstract: PubMed


12.1.3 Toxicity Summary

The intravenous LD\textsubscript{50} of phylloquinone in the mouse is 41.5 and 52 mL/kg for the 0.2\% and 1\% concentrations, respectively.

12.1.4 Human Toxicity Excerpts

/HUMAN EXPOSURE STUDIES/ To determine whether vitamin K administration affects urinary calcium excretion in postmenopausal women. Before- and after-trials with a 2-week treatment period. Healthy postmenopausal women (55 to 75 years old) were recruited from the convents in and around Maastricht. Controls (25 to 40 years old) were healthy premenopausal volunteers. Daily administration of 1 mg of vitamin K for 2 weeks. Serum immunoreactive osteocalcin: hydroxylapatite binding (HAB) capacity of serum immunoreactive osteocalcin; excretion of calcium, hydroxyproline, and creatinine in the urine during the last 2 h of a 16-h fasting period. In premenopausal women, no effect of vitamin K administration was seen. In the postmenopausal group, vitamin K induced increased serum immunoreactive osteocalcin concentration; normalization of the HAB capacity of serum immunoreactive osteocalcin; this marker was less than 50\% that of the controls in the pretreatment samples); a decrease in urinary calcium excretion, notably in the “fast losers” of calcium; and a parallel decrease in urinary hydroxyproline excretion in the fast losers of calcium. The serum immunoreactive osteocalcin level may vary with vitamin K status. This variance should be taken into consideration if osteocalcin is used as a marker for osteoblast activity. Vitamin K is one factor that may play a role in the loss of bone mass in postmenopausal osteoporosis.


/EPIDEMIOLOGY STUDIES/ A retrospective review of anaphylaxis after i.v. phytonadione over a 58-month period at a large academic center was performed. During the period of the study a protocol for the administration of i.v. phytonadione was in place. A review of computerized records and survey of staff identified cases of anaphylaxis meeting predefined inclusion criteria. In addition, a literature review was performed for articles concerning anaphylaxis after i.v. phytonadione. Over the 58 months of the study, a total of 6,572 doses of i.v. phytonadione were administered. Two cases of anaphylaxis after i.v. phytonadione were identified. The incidence of anaphylaxis was 3 per 10,000 doses with 95\% confidence intervals of 0.04 to 11 per 10,000 doses. The literature review identified 14 cases meeting inclusion criteria with no reviews of the literature or estimates of incidence. The incidence of anaphylaxis after i.v. phytonadione is overall comparable or slightly less than other drugs known to cause anaphylaxis.


12.1.5 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ The offspring of mice treated with...
Phylloquinone by injection had cleft lip and exencephaly. Six pregnant Sprague-Dawley rats were dosed with 10 mg/kg body weight phylloquinone (Konakion) daily on days 9-20 of gestation, and the fetuses were delivered on day 21 and examined for external malformations and the presence of hemorrhages only. No adverse effects were noted when compared with a group of five untreated controls.


Phytonadione/ ... at concentrations up to 2,000 mcg/plate with or without metabolic activation, was negative in the Ames microbial mutagen test.

Medical Economics Co; Physicians Desk Reference 56th ed p.2130 (2002)

Phylloquinone/ ... enhanced the frequency of sister chromatid exchange in cultured human maternal lymphocytes at concentrations that are relevant in vivo, and a similar increase in sister chromatid exchange frequency was observed in cultured lymphocytes from human placental blood.


12.1.6 Non-Human Toxicity Values

LD50 Mouse oral 25 g/kg


LD50 Mouse subcutaneous 1000 mg/kg


12.1.7 Populations at Special Risk

SRP: Persons with bleeding disorders or who are taking anticoagulants should be protected from exposure.

from HSDB
12.2 Ecological Information

12.2.1 Natural Occurring Sources

FAT-SOL VIT OCCURRING NATURALLY AS TRANS ISOMER. ... FIRST ISOLATED FROM ALFALFA; ALSO SHOWS WIDESPREAD DISTRIBUTION IN HIGHER GREEN PLANTS: DAM ET AL, HELV CHIM ACTA 22, 310 (1939).


Phylloquinone is widely distributed in higher plants and in some blue-green algae. It is present in many foods, especially leafy green vegetables and some vegetable oils.

13 Literature

13.1 Depositor Provided PubMed Citations

CLICK TO LOAD...

13.2 NLM Curated PubMed Citations

CLICK TO LOAD...

13.3 Synthesis References


from Human Metabolome Database (HMDB)

13.4 Metabolite References

1 to 1 of 1
<table>
<thead>
<tr>
<th>PMID</th>
<th>Reference</th>
</tr>
</thead>
</table>

13.5 Springer Nature References

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14 Patents

14.1 Depositor-Supplied Patent Identifiers

CLICK TO LOAD...

› from PubChem
15 Biomolecular Interactions and Pathways

15.1 Protein Bound 3-D Structures

CLICK TO LOAD...

15.2 DrugBank Interactions

<table>
<thead>
<tr>
<th>Target</th>
<th>Vitamin K-dependent gamma-carboxylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>inducer</td>
</tr>
<tr>
<td>PubChem Protein Target</td>
<td>P38435</td>
</tr>
<tr>
<td>PubChem Gene Target</td>
<td>GGCX</td>
</tr>
<tr>
<td>General Function</td>
<td>Gamma-glutamyl carboxylase activity</td>
</tr>
<tr>
<td>Specific Function</td>
<td>Mediates the vitamin K-dependent carboxylation of glutamate residues to calcium-binding gamma-carboxyglutamate (Gla) residues with the concomitant conversion of the reduced hydroquinone form of vitamin K to vitamin K epoxide.</td>
</tr>
</tbody>
</table>

| Target | Osteocalcin |
| Action | agonist |
| PubChem Gene Target | BGLAP |
| General Function | Structural molecule activity |
| Specific Function | Constitutes 1-2% of the total bone protein. It binds strongly to apatite and calcium. |

16 Biological Test Results

16.1 BioAssay Results

CLICK TO LOAD...
17 Classification

17.1 Ontologies

17.1.1 MeSH Tree

CLICK TO LOAD...

from MeSH

17.1.2 ChEBI Ontology

CLICK TO LOAD...

from ChEBI

17.1.3 LIPID MAPS Classification

CLICK TO LOAD...

from LIPID MAPS
17.1.4 WHO ATC Classification System

CLICK TO LOAD...

◇ from WHO ATC

17.1.5 WIPO IPC

CLICK TO LOAD...

◇ from WIPO

17.1.6 ChemIDplus

CLICK TO LOAD...

◇ from ChemIDplus
18 Information Sources

1. ChemIDplus /source/ChemIDplus
   Phytonadione [USP:JAN]
   Vitamin K1
   (R*,R*-(E))-(1)-2-Methyl-3-(3,7,11,15-tetramethylhexadec-2-enyl)-1,4-naphthoquinone
   ChemIDplus Chemical Information Classification

2. DTP/NCI /source/DTP/NCI
   Phytonadione

3. DrugBank /source/DrugBank
   Phylloquinone
   http://www.drugbank.ca/drugs/DB01022
   http://www.drugbank.ca/drugs/DB01022#targets

4. EPA DSStox /source/EPA DSStox
   Phytonadione
   https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8023472

   [R*,R*-(E)]-(±)-2-methyl-3-(3,7,11,15-tetramethylhexadec-2-enyl)-1,4-naphthoquinone
   https://echa.europa.eu/
   Phytomenadione

6. Human Metabolome Database (HMDB) /source/Human Metabolome Database (HMDB)
   Reduced Vitamin K (phylloquinone)
   http://www.hmdb.ca/metabolites/HMDB0004198
   Phytonadione
   http://www.hmdb.ca/metabolites/HMDB0015157

7. ClinicalTrials.gov /source/ClinicalTrials.gov
   Phytonadione
   https://clinicaltrials.gov/

   PHYTONADIONE
   VITAMIN K
   ALPHA-TOCOPHEROL ACETATE; ASCORBIC ACID; BIOTIN; CHOLECALCIFEROL; CYANOCOBALAMIN;
   DEXPANTHENOL; FOLIC ACID; NIACINAMIDE; PYRIDOXINE HYDROCHLORIDE; RIBOFLAVIN 5'-PHOSPHATE
   SODIUM; THIAMINE HYDROCHLORIDE; VITAMIN A PALMITATE; VITAMIN K

VITAMIN K1 | C31H46O2 - PubChem
https://pubchem.ncbi.nlm.nih.gov/compound/Phylloquinone#section=18
vitamin k1

16. WHO ATC /source/WHO ATC
https://www.whocc.no/atc/ https://www.whocc.no/atac/
ATC Code
https://www.whocc.no/atc_ddd_index/ https://www.whocc.no/atc_ddd_index/

(E)-phytonadione

18. PubChem
Data deposited in or computed by PubChem

19. MeSH /source/MeSH
Vitamin K 1
MeSH Tree
Vitamins
Antifibrinolytic Agents

20. ChEBI /source/ChEBI
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21. LIPID MAPS /source/LIPID MAPS
LIPID MAPS classification system for lipids

22. WIPO /source/WIPO
International Patent Classification
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23. NCBI
LinkOut is a service that allows one to link directly from NCBI databases to a wide range of information and services beyond NCBI systems.