SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dindevan 25mg Tablets
Phenindione 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg phenindione

Excipient with known effect:
Each tablet contains 72mg lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Green flat, bevel-edged uncoated tablets, scored on one side, engraved D25 on the scored side.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dindevan (Phenindione BP) is a synthetic anticoagulant which acts by interfering with the formation of clotting factors II, VII, IX and X. It produces its effect in 36-48 hours after the initial dose; the effect wanes over a period of 48-72 hours after Dindevan is stopped.

Anticoagulant therapy can be initiated with Heparin and Dindevan together.

Anticoagulant therapy in the prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.

Prophylaxis after insertion of prosthetic heart valves.

Prophylaxis and treatment of venous thrombosis and pulmonary embolism.

4.2 Posology and method of administration

Posology:

Adults: Initial loading dose of 200mg, followed on the second day by a dose of 100mg. Dosage must be adjusted from the third day, dependent on the results of the appropriate coagulation tests such as prothrombin time, reported as international normalised ratio (INR).

Note: Concomitant heparin therapy affects the results of INR control tests, and heparin should be discontinued at least 6 hours before the first INR control test is undertaken.

Control tests must be undertaken at regular intervals and the dosage adjusted according to the results of the INR tests.
A maintenance dose of 50-150mg/day is satisfactory in most patients, but a "resistant" patient may need 200mg/day or more.
A "sensitive" patient may need less than 50mg/day.

Method of administration
Oral

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Haemorrhagic stroke (see section 4.4 for further details)
- Clinically significant bleeding
- Within 72 hours of major surgery with risk of severe bleeding (for information on other surgery, see section 4.4)
- Within 48 hours postpartum
- Pregnancy (see section 4.6)
- Lactation: Infants should not be fed with breast milk from mothers being treated with Dindevan.
- Drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)
- Dindevan should not be given to patients with severe renal or hepatic disease, bacterial endocarditis, actual or potential haemorrhagic conditions, or to patients with uncontrolled hypertension

4.4 Special warnings and precautions for use

Most adverse events reported with Dindevan are a result of allergic reactions or over anticoagulation therefore it is important that the need for therapy is reviewed on a regular basis and therapy discontinued when no longer required.
Patients should be made aware of the symptoms of allergic reactions and told to seek medical advice if they experience any signs of allergic reactions.

Patients should be given a patient-held information booklet ('anticoagulant card') and informed of symptoms for which they should seek medical attention.
The following may exaggerate the effects of Dindevan and require a reduction of dosage:

- Loss of weight
- Elderly patients
- Acute illnesses
- Deficient renal function
- Decreased dietary intake of Vitamin K
- Administration of certain drugs (see section 4.5)

The following may reduce the effects of Dindevan and may require the dosage to be increased:

- Weight gain
- Diarrhoea and vomiting
- Increased intake of Vitamin K, fats or oils
- Administration of certain drugs (See section 4.5)

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking vitamin K antagonists, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with Dindevan.

Monitoring
When Dindevan is started using a standard dosing regimen, the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilized in the target range, the INR can be determined at longer intervals.
INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease.
Patients for whom adherence may be difficult should be monitored more frequently.

Thrombophilia
Patients with protein C deficiency are at risk of developing skin necrosis when starting Dindevan treatment. In patients with protein C deficiency, therapy should be introduced without a loading dose of Dindevan even if heparin is given. Patients with protein S deficiency may also be at risk and it is advisable to introduce Dindevan therapy slowly in these circumstances.

Risk of haemorrhage
The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Dindevan should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0),

age ≥65, highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs (see section 4.5). All patients treated with Dindevan should have INR monitored regularly. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed on measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding.
Checking the INR and reducing or omitting doses depending on INR level is essential, following consultation with anticoagulation services if necessary. If the INR is found to be too high, reduce dose or stop Dindevan treatment; sometimes it will be necessary to reverse anticoagulation. INR should be checked within 2–3 days to ensure that it is falling.
Any concomitant anti-platelet drugs should be used with caution due an increased risk of bleeding.

Haemorrhage
Haemorrhage can indicate an overdose of Dindevan has been taken. For advice on treatment of haemorrhage see section 4.9.
Unexpected bleeding at therapeutic levels should always be investigated and INR monitored.

Ischemic stroke
Anticoagulation following an ischaemic stroke increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation, long term treatment with Dindevan is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Dindevan treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. In patients with large embolic strokes or uncontrolled hypertension, Dindevan treatment should be stopped for 14 days.

Surgery
For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5. For surgery where there is a risk of severe bleeding, Dindevan should be stopped 3 days prior to surgery.
Where it is necessary to continue anticoagulation e.g. risk of life-threatening thromboembolism, the INR should be reduced to <2.5 and heparin therapy should be started.
If surgery is required and Dindevan cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.
The timing for re-instating Dindevan therapy depends on the risk of postoperative haemorrhage. In most instances Dindevan treatment can be restarted as soon as the patient has an oral intake.
Administration of Vitamin K can lead to resistance to the action of Dindevan for some days. For this reason, fresh-frozen plasma should be administrated to patients with prosthetic heart valves when haemorrhage has occurred.

Dental Surgery
Dindevan need not be stopped before routine dental surgery e.g. tooth extraction.

Active peptic ulceration
Due to a high risk of bleeding, patients with active peptic ulcers should be treated with caution. Such patients should be reviewed regularly and informed of how to recognise bleeding and what to do in the event of bleeding occurring.

Interactions
Many drugs and foods interact with Dindevan and affect the prothrombin time (see section 4.5). Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations.

Thyroid disorders
Patients with hyper- or hypo-thyroidism should be closely monitored on starting Dindevan therapy.

Additional circumstances where changes in dose may be required
Acquired or inherited Dindevan resistance should be suspected if larger than usual daily doses of Dindevan are required to achieve the desired anticoagulant effect.

Genetic information
Genetic variability particularly in relation to VKORC1 can significantly affect dose requirements for Dindevan. If a family association with this polymorphism is known extra care is warranted.

Dindevan contains Lactose
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose–galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Care is required with all concomitant therapy with Dindevan. The individual product information for any new concomitant therapy should be consulted for specific guidance on Dindevan dose adjustment and therapeutic monitoring. If no information is provided the possibility of an interaction should be considered.
Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

Pharmacodynamic interactions Drugs which are contraindicated
Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of Dindevan, increasing the risk of bleeding.
Fibrinolytic drugs such as streptokinase and alteplase are contra-indicated in patients receiving Dindevan.
Drugs which should be avoided if possible
The following examples should be avoided, or administered with caution with increased clinical and laboratory monitoring:

- Clopidogrel
- NSAIDs (including aspirin and cox-2 specific NSAIDS)
- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Unfractionated heparins and heparin derivatives, low molecular weight heparins
- Fondaparinux, rivaroxaban
- Glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- Prostacyclin
- SSRI and SNRI antidepressants
- Clofibrate
- Miconazole
- Antineoplastics
- Other drugs which inhibit haemostasis, clotting or platelet action

Low-dose aspirin with Dindevan may have a role in some patients but the risk of gastrointestinal bleeding is increased.

Listed below are drugs which are known to interact with Dindevan in a clinically significant way.

Examples of drugs which potentiate the effect of Dindevan

- ACTH, allopurinol, amitriptyline/nortriptyline, Cimetidine, Dextropropoxyphene, Glucagon, Hepato-toxic drugs, Phenformin, Thyroid compounds, Tolbutamide
- Disulfiram, amiodarone, propafenone, anabolic steroids, corticosteroids, oral contraceptives, zafirlukast.

Examples of drugs which antagonise the effect of Dindevan

Barbiturates, Carbamazepine; Griseofulvin, Phenytoin.

Other drug interactions

Broad spectrum antibiotics may potentiate the effect of Dindevan by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K. Cholestyramine and sucralfate potentially decrease absorption of Dindevan. Increased INR has been reported in patients taking glucosamine and other anticoagulant (e.g. warfarin) and the potential for similar effect exists with Dindevan, accordingly this combination is not recommended.

Interactions with herbal products

Many herbal products have a theoretical effect on Dindevan. Patients should generally avoid taking any herbal medicines or food supplements whilst taking Dindevan and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Interactions with food and food supplements

Individual case reports suggest a possible interaction between other anticoagulant (e.g. warfarin) and cranberry juice, in most cases leading to an increase in INR or bleeding event. The possibility of similar occurrence with

Dindevan may exist. Increased supervision and INR monitoring should be considered for any patient taking Dindevan and regular cranberry juice.
Certain foods such as liver, broccoli, brussels sprouts and green leafy vegetables contain large amounts of vitamin K. Sudden changes in diet can potentially affect control of anticoagulation. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet.
Many other food supplements have a theoretical effect on Dindevan; however most of these interactions are not proven. Patients should generally avoid taking any food supplements whilst taking Dindevan, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Laboratory tests
Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test.

4.6 Fertility, pregnancy and lactation

Pregnancy
Oral anticoagulant therapy is contraindicated in pregnancy because of possible teratogenicity and the risk of foetal haemorrhage near term.
It is suggested that heparin, which does not cross the placenta, can be used during the first trimester and after 37 weeks of gestation. However, the use of heparin during pregnancy is not absolutely safe and specialist guidance should be obtained for patients who are pregnant and who need anticoagulant therapy.
Women of child-bearing age who are treated with Dindevan should be cautioned about the possible complications of pregnancy.

Breast-feeding
As Dindevan is distributed into breast milk, infants should not be fed with breast milk from mothers being treated with Dindevan (see section 4.3).

Fertility
No data available.

4.7 Effects on ability to drive and use machines
Dindevan has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data)

The following undesirable effects have been reported:

System organ class database	**Frequency**	**Adverse reactions**
Infections and infestations	Not known	Fever
Blood and lymphatic system disorders	Not known	leucopenia; agranulocytosis*; lymphadenopathy*; eosinophilia*; Leukocytosis*; Pancytopenia*; leukaemoid syndrome*
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Not known	Cerebral haemorrhage; cerebral subdural haematoma
Vascular disorders	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Not known	Haemothorax, epistaxis
Gastrointestinal disorders	Not known	Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena; Dysgeusia
Hepatobiliary disorders	Not known	Hepatitis, jaundice*
Skin and subcutaneous tissue disorders	Not known	Rash*, purpura; Blue toe syndrome; ecchymosis; alopecia*; skin necrosis*; dermatitis exfoliative*, exanthema.
Renal and Urinary disorders	Not known	Haematuria; renal damage with tubular necrosis*; albuminuria*
Investigations	Not known	Haematocrit decreased; haemoglobin decreased

*These events have been reported in relation to hypersensitivity reactions. If any of the above effects are found, Dindevan therapy should be stopped immediately, and a full investigation of blood, liver and renal function should

be undertaken. Possible sensitivity to other drugs should be considered. Other anticoagulants, such as warfarin, are tolerated usually by patients sensitive to Dindevan.

An episode of bleeding during anticoagulant therapy must be investigated fully and not regarded automatically as a manifestation of overdosage. The metabolites of Dindevan often colour the urine pink or orange. This effect may be distinguished from discoloration caused by haemoglobin by the addition of a few drops of dilute acetic acid to the urine. If the discoloration is due to Dindevan, the discoloration will disappear immediately.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
As it may take 48-72 hours for the anticoagulant effect to develop fully, the onset of bleeding may be delayed for a few days and patients may remain profoundly anti-coagulated for several days. Spontaneous bruising, haematomas, haematuria, rectal bleeding and haemorrhage into any internal organ may occur.

Management
- The benefit of gastric decontamination is uncertain. If the patient presents within one hour of ingestion of more than 0.25mg/kg or more than the patient's therapeutic dose, consider activated charcoal (50g for adults).
- Measure the prothrombin time at presentation and sequentially every 24 -48 hours after ingestion depending on the initial dose and initial INR.

For patients ON long-term phenindione therapy:
- Monitor INR for at least 48 hours post overdose.
- If there is no active bleeding but the prothrombin time is dangerously prolonged (INR >6.0), give 0.5-1mg vitamin K by slow IV infusion. Further doses may be given as necessary, titrated to INR. Large doses of Vitamin K may completely reverse the effects of phenindione and make it difficult to re-establish anticoagulation.
- If there is active bleeding give fresh frozen plasma and vitamin K 1mg by slow IV infusion. Titrate further treatment according to repeat INR and presence of active bleeding.

- In cases of life-threatening haemorrhage use fresh frozen plasma or factor concentrate.
- Monitor INR to determine when to restart normal therapy.

For the patients NOT ON long-term phenindione therapy:

- If the INR remains normal for 24-48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.
- If there is no active bleeding and the patient has ingested more than 0.25mg/kg or the prothrombin time is already significantly prolonged (INR >6.0) give vitamin K_1. The adult dose is 10-20mg orally or by slow iv infusion. Delay oral vitamin K_1 at least 4 hours after any activated charcoal has been given. Daily doses may be necessary until the prothrombin time returns to the normal range.
- In active bleeding give fresh frozen plasma and vitamin K_1 10-20mg for an adult by slow intravenous injection.
- If life-threatening haemorrhage, use fresh frozen plasma or a factor concentrate.

Monitor the INR to determine when to stop vitamin K_1.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic Vitamin K antagonists
ATC code: B01AA02

Mechanism of action
Dindevan is a synthetic anticoagulant which acts by interfering with the formation of certain clotting factors. It produces its effect in 36-48 hours after the initial dose. The effect wanes after a period of 48-72 hours after Dindevan is stopped.

5.2 Pharmacokinetic properties

Phenindione has been quantified by polarography, which has a limit of detection of 4mg/l. Following intravenous administration of 5mg/kg Phenindione to six subjects over a period of 2-3 months, the rate of decline in plasma levels of the drug averaged 10% per hour, corresponding to a half-life of 5-6 hours.

Absorption
Absorption of oral Phenindione in 12 subjects was rapid, with peak plasma levels being attained in 1-3 hours.

Distribution
In three subjects given the same dose intravenously, plasma levels were identical to those following oral administration, indicating complete absorption.

Biotransformation
Plasma levels of Phenindione following a single 400mg dose in 10 subjects were related to prothrombin response. There was a delay of 8-12 hours before any prothrombin response could be detected. All subjects showed a detectable prothrombin time increase within 24 hours. In 9 out of 10 subjects the prothrombin response was maximal two days after dosage, and in one subject three days after dosage.

Elimination
Prothrombin times in all 10 subjects did not return to control values until at least four days after dosage. Although there was no correlation among different individuals between the maximum prothrombin response and the plasma levels of phenindione, the duration of prothrombin response reflected the rate at which the drug disappeared from the plasma.
Following repeated dosage with 50-150mg per day for periods of three weeks to five months, no accumulations of phenindione was observed, although a satisfactory maintenance of prothrombin response was obtained.

5.3 Preclinical safety data
No further relevant data

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch maize BP

Lactose BP

Anhydrous citric acid powder BP

Magnesium stearate BP

Purified water BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
18 Months (Unopened)

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Polypropylene container with a tamper evident, low density polyethylene cap containing 28, 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharma Group Ltd.,

Dashwood House, 69 Old Broad Street,

London, EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10972/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/10/1993

10 DATE OF REVISION OF THE TEXT

19/02/2024