

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dindevan 50mg tablets

Phenindione Tablets 50mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg phenindione

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dindevan (Phenindione BP) is a synthetic anticoagulant which acts by interfering with the formation of 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

Dosage:

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.

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

Control tests must be undertaken at regular intervals and the dosage adjusted according to the results of the 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 product or any of the excipients
- 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
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose–galactose malabsorption should not take this medicine

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)

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. Dabigatran 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, Dabigatran 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, Dabigatran 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 Dabigatran cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.

The timing for re-instating Dabigatran therapy depends on the risk of post operative haemorrhage. In most instances Dabigatran treatment can be re-started as soon as the patient has an oral intake

Administration of Vitamin K can lead to resistance to the action of Dabigatran for some days. For this reason, fresh-frozen plasma should be administered to patients with prosthetic heart valves when haemorrhage has occurred.

Dental Surgery

Dabigatran 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 Dabigatran 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 Dabigatran therapy.

Additional circumstances where changes in dose may be required

Acquired or inherited Dabigatran resistance should be suspected if larger than usual daily doses of Dabigatran are required to achieve the desired anticoagulant effect.

Genetic information

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

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
- 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, metronidazole, anabolic steroids, corticosteroids

Examples of drugs which antagonise the effect of Dindevan

Carbamazepine, Colestyramine, griseofulvin, rifampicin, 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. Colestyramine 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 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 patient's 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.

Lactation

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).

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

The following undesirable effects have been reported:

Hypersensitivity including skin rashes, alopecia, exanthema, skin necrosis, exfoliative dermatitis, leucopenia and agranulocytosis, hepatitis and renal damage with tubular necrosis. Micro-adenopathy, jaundice, albuminuria, eosinophilia, a leucaemoid blood picture, and cytopenia may be observed.

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.

As with other anticoagulants (e.g. warfarin) following undesirable effects can occur:

- Other Skin and subcutaneous disorders include purpura; 'purple toes' syndrome; erythematous swollen skin patches leading to ecchymosis
- Infections and infestations: Fever
- Nervous system disorders: Cerebral haemorrhage; cerebral subdural haematoma
- Vascular disorders: Haemorrhage
- Respiratory, thoracic and mediastinal disorders: Haemothorax, epistaxis
- Gastrointestinal disorders: Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena; taste disturbances have also been reported
- Renal and Urinary disorders: Haematuria
- Investigations: Unexplained drop in haematocrit; haemoglobin decreased

An episode of bleeding during anticoagulant therapy must be investigated fully and not regarded automatically as a manifestation of overdose. 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.

4.9 Overdose

Symptoms of Overdose:

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; 1g/kg for children).

- 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 K₁. The adult dose is 10-20mg orally or by slow iv infusion, (250 micrograms/kg body weight for a child). Delay oral vitamin K₁ 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 K₁ 10-20mg for an adult by slow intravenous injection (250 micrograms/kg body weight for a child).
- If life-threatening haemorrhage, use fresh frozen plasma or a factor concentrate.
- Monitor the INR to determine when to stop vitamin K₁.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 of oral Phenindione in 12 subjects was rapid, with peak plasma levels being attained in 1-3 hours. In three subjects given the same dose intravenously, plasma levels were identical to those following oral administration, indicating complete absorption.

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. 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

None stated

6.3 Shelf life

9 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 Dindevan 50mg tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Goldshield Group Limited
Trading as: Goldshield Pharmaceuticals
NLA Tower
12-16 Addiscombe Road
Croydon
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CR0 0XT
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PL 10972/0039

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01/06/2011