SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOXIUM® 500
500 mg, capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 hard capsule contains 500 mg of calcium dobesilate monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard
Opaque capsules with a yellow capsule body and a dark green cap

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Microangiopathies, in particular diabetic retinopathy.
Clinical signs of chronic venous insufficiency in the lower limbs (pain, cramps, paresthesia, oedema, stasis dermatosis), as adjuvant in superficial thrombophlebitis. Haemorrhoidal syndrome, microcirculation disorders of arteriovenous origin.

4.2 Posology and method of administration

Posology
For adults only
Generally 500 to 1000 mg – 1 capsule once or twice a day
Dosage should be adapted individually according to the severity of the case. Treatment duration, which is generally between a few weeks and several months, depends on the disease and its evolution.

Renal impairment
The safety and efficacy of calcium dobesilate have not been studied in patients with renal impairment. Since the drug is excreted by the urinary route, caution is required in case of renal insufficiency. Thus, the dose may be reduced when administering Doxium 500 to these patients, especially in patients with severe renal insufficiency requiring dialysis.

Hepatic impairment

The safety and efficacy of calcium dobesilate have not been studied in patients with hepatic impairment. Thus, caution is required when administering Doxium 500 to these patients.

Method of administration
Doxium 500 is designed for oral administration. Doxium 500 should be taken during or right after meals, to minimise any gastric discomfort.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The dose may be reduced in case of severe renal insufficiency requiring dialysis.

In very rare cases, administration of calcium dobesilate may induce agranulocytosis (see section 4.8). In this situation, the symptoms may include high fever, infections of the oral cavity (tonsillitis), sore throat, anogenital inflammation and other symptoms that are common signs of infection. If any of these symptoms appear the treatment must be stopped. It is then essential to assess the blood formula and leucogram immediately.

Doxium 500 may trigger severe hypersensitivity reactions (anaphylactic reaction or shock). In case of hypersensitivity reactions, the treatment must be stopped.

Older people
The elderly population was broadly represented in the clinical studies with calcium dobesilate and no overall safety concerns emerged.

Paediatric population
No trials have been conducted for studying the use of calcium dobesilate in the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products are known.
At therapeutic doses calcium dobesilate may interfere with creatinine enzymatic assay resulting in values lower than those expected.
During the course of calcium dobesilate treatment, sample collection (e.g. blood sampling) required for laboratory testing should be done before the first daily administration of the drug in order to minimise any potential interaction of calcium dobesilate with laboratory testing.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of calcium dobesilate in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of calcium dobesilate during pregnancy.

Breast-feeding
Calcium dobesilate enters the maternal milk in very small quantities (0.4 µg/ml after intake of 3 x 500 mg). Administration of Doxium 500 is not indicated during breast-feeding. As a precaution, either the treatment or the breast-feeding should be stopped.

Fertility
Based on present studies, calcium dobesilate did not show any overt toxic effect on reproduction.

4.7 Effects on ability to drive and use machines

Doxium 500 has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are classified according to MedDRA system organ class, and by frequency, as follows:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10000 to < 1/1000)
Very rare (< 1/10000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Very rare: agranulocytosis (see section 4.4)
Not known: neutropenia, leukopenia

Immune system disorders
Uncommon: hypersensitivity (rash, allergic dermatitis, pruritus, urticaria, face oedema; see section 4.4)
Very rare: anaphylactic reaction (see section 4.4)

Nervous system disorders
Common: headache

Gastrointestinal disorders
Common: abdominal pain, nausea, diarrhoea, vomiting

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia

General disorders and administration site conditions
Uncommon: pyrexia, chills, asthenia, fatigue

Investigations
Common: alanine aminotransferase increase

These reactions are generally reversible once treatment is stopped.

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

ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

4.9 Overdose

No case of overdose has been reported and clinical signs of overdose are not known. Overdose should be treated according to standard medical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other sclerosing agents
ATC code: C05BX01

Regulator of capillary functions.
Calcium dobesilate acts on the capillary walls by regulating its impaired physiological functions - increased permeability and decreased resistance. It increases erythrocyte flexibility, inhibits platelet hyperaggregation and, in diabetic retinopathy, it reduces plasma and blood hyperviscosity, thus improving blood rheological properties and tissue irrigation. These effects allow to correct capillary dysfunctions either of functional origin or caused by constitutional or acquired metabolic disorders. Calcium dobesilate contributes to reduce oedema.

5.2 Pharmacokinetic properties

After oral administration of 500 mg of calcium dobesilate, its blood level is above 6 µg/ml between the 3rd and 10th hour, with a maximum (Cmax) of 8 µg/ml on the average after 6 hours (tmax). Twenty four hours after intake blood level is about 3 µg/ml. The rate of protein-binding is 20 - 25 %. In animals, calcium dobesilate does not cross the haematoencephalic or the placental barrier, but it is not known whether

this is also the case in humans. Calcium dobesilate enters the maternal milk in very low quantities (0,4 µg/ml after intake of 1500 mg as observed in one study).
Calcium dobesilate does not enter the enterohepatic cycle and is excreted mainly unchanged with only 10 % being excreted as metabolites. About 50 % of the orally administered dose are eliminated in the first 24-hour urine and about 10 % in the faeces.
Plasma half-life is around 5 hours.

Kinetics in particular clinical situations
It is not known to what extent renal function disorders influence the pharmacokinetic properties of calcium dobesilate (see section 4.2 and 4.4).

5.3 Preclinical safety data

Acute and chronic toxicity studies, foetotoxicity and mutagenicity studies on calcium dobesilate have not revealed any toxic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, maize starch;
Capsule shell's composition: gelatin, yellow ferric oxide (E 172), indigotine (E 132), titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Transparent, colourless, hard, shiny aluminium, printed PVC/PVDC blister

Pack of 30 capsules, hard
Pack of 60 capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

OM PHARMA S.A.
Rua de Industria, 2 – Quinta Grande
2610-088 Amadora – Lisboa - Portugal

8. MARKETING AUTHORISATION NUMBER

MA121/00501

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 20, 2006

10. DATE OF REVISION OF THE TEXT

Month Year