

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/133/001

Case No: 2074339

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Dona 1500mg Powder for Oral Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/02/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dona 1500mg Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains	
Crystalline glucosamine sulfate	1884mg
equivalent to : glucosamine sulfate	1500mg
sodium chloride	384mg

Excipients: contains aspartame (E951) and sorbitol (E420)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Solution

Product imported from the Italy
A white, crystalline, odourless powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of the symptoms of osteoarthritis, i.e. pain and function limitation.

4.2 Posology and method of administration

Adults and the Elderly:

The contents of one sachet (dissolved in a glass of water) should be taken once daily, preferably at meals.

Pivotal proof of efficacy has been demonstrated for periods of up to three months, with a residual effect evident for two months after drug withdrawal. The safety and efficacy of the product were also confirmed in pivotal clinical trials for treatment up to three years. Continuous treatment beyond 3 years cannot be recommended as the safety has not been established beyond this period.

Children:

Safety and efficacy has not been established in children, therefore no dosage recommendations can be made.

4.3 Contraindications

Hypersensitivity to glucosamine. The powder for oral solution contains aspartame and is therefore contraindicated in patients with phenylketonuria.

4.4 Special warnings and precautions for use

Since glucosamine is obtained from shellfish, patients who are allergic to shellfish should exercise caution in the use of the product.

This medicinal product contains 151 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Caution is advised in treatment of patients with impaired glucose tolerance. Closer monitoring of blood sugar levels may be necessary in diabetics at the beginning of treatment.

No special studies were performed in patients with renal or hepatic insufficiency. The toxicological and pharmacokinetic profile of the product does not indicate limitations for these patients. However, administration to patients with severe hepatic or renal insufficiency should be under medical supervision.

The powder for oral solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this pharmaceutical form.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed, however, the physico-chemical and pharmacokinetic properties of glucosamine sulfate suggest a low potential for interactions. The compound does not compete for absorption mechanisms and, after absorption, does not bind to plasma protein, while its metabolic fate as an endogenous substance incorporated in proteoglycans or degraded independently of the cytochrome enzyme system, is unlikely to give rise to drug interactions.

However, an increased effect of warfarin during concomitant treatment with glucosamine has been reported in post-marketing experience. Therefore, more frequent measurement of the warfarin effect may be considered.

The oral administration of glucosamine sulphate can enhance the gastrointestinal absorption of tetracyclines.

4.6 Pregnancy and lactation

In animal studies, no unfavourable effects on reproductive function or on lactation were demonstrated. In the absence of such studies in humans, the use of glucosamine sulfate during pregnancy and lactation should be limited to cases where the benefits outweigh the potential risks. Administration during the first three months of pregnancy must be avoided.

4.7 Effects on ability to drive and use machines

No effects on the CNS or motor system are known that might impair the ability to drive or use machines.

4.8 Undesirable effects

The more commonly observed undesirable effects after oral administration are stomach pain, flatulence, constipation and diarrhoea.

In the following table, adverse reactions have been grouped on the basis of “Internationally agreed Order of Importance” System Organ Class (SOC) MedDRA Classification. In each SOC, undesirable effects were classified according to their occurrence frequency. In each frequency class the undesirable effects are reported according to an decreasing order of severity.

System Organ Class	Very common ≥ 1/10	Common from ≥ 1/100 to ≤ 1/10	Uncommon from ≥1/1,000 to ≤ 1/100	Rare from ≥ 1/10,000 to ≤ 1/1,000	Very rare ≤ 1/10,000	Unknown*
Immune system disorders						Allergic reaction
Nervous system disorders		Headache Somnolence				
Eye disorders						Visual disturbance
Gastrointestinal disorders		Diarrhoea Constipation Nausea Flatulence Stomach pain Dyspepsia				
Skin and subcutaneous tissue disorders			Erythema Pruritus Rash			Hair loss

* which frequency cannot be estimated by the available data

4.9 Overdose

No cases of accidental or intentional overdose are known. The animal acute and chronic toxicological studies indicate that toxic effects and symptoms are unlikely to occur at doses up to 200 times the therapeutic dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Product for the treatment of osteoarthritis.
(Product for the musculoskeletal system - ATC code: M01AX05).

Glucosamine sulfate, the active ingredient of DONA, is a chemically well defined and pure compound and is the salt of the natural amino-monosaccharide glucosamine which is physiologically present in the human body.

The mechanism of action of glucosamine sulfate in osteoarthritis is unknown. However, glucosamine is a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. In vitro and in vivo studies have shown that glucosamine sulfate stimulates the synthesis of physiological glycosaminoglycans and proteoglycans by chondrocytes and of hyaluronic acid by synoviocytes.

Glucosamine sulfate has also been shown to inhibit the activity of cartilage-destroying enzymes such as collagenase and phospholipase A2, as well as the generation of other tissue-damaging substances such as superoxide radicals, or the activity of lysosomal enzymes. These activities may contribute to the mild anti-inflammatory effects observed in vivo in experimental models, including some types of experimental arthritis. Unlike NSAIDs, glucosamine sulfate does not inhibit the synthesis of prostaglandins.

No effects on the cardiovascular and respiratory systems, on the CNS, or the autonomic nervous system, have been shown in safety pharmacology studies.

Pivotal proof of efficacy has been demonstrated in knee osteoarthritis, and has been partly replicated in osteoarthritis of the spine and of other joints, including the hip. The efficacy of glucosamine sulfate has not been established for osteoarthritis of the hand.

Evidence of efficacy and safety has been obtained after long-term (three years) treatment in knee osteoarthritis patients.

Analgesics and NSAIDs may be used concomitantly with glucosamine sulfate, either for rescue analgesia during possible flares of the disease, or in the initial period of treatment, when the symptomatic effects of glucosamine sulfate may be delayed for 1-2 weeks. Physical therapy programs can be used concomitantly with glucosamine sulfate in the overall management of osteoarthritis.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of glucosamine sulfate have been studied in the rat and dog using uniformly ^{14}C -labelled glucosamine. Following intravenous administration, radiolabelled glucosamine disappears rapidly from blood and is incorporated into various tissues, in particular the liver, kidney and the articular cartilage. In the latter, the radioactivity from labelled glucosamine remains for a prolonged period of time, with a biological half life of about 70 hours. About 50% of the administered radioactivity is exhaled as CO_2 during the 6 days following the administration, 30-40% is found in the urine, whereas the excretion via the faeces is only about 2%.

After oral administration, radiolabelled glucosamine is rapidly and almost completely absorbed. The subsequent pharmacokinetic and metabolic patterns are consistent with those after intravenous administration.

A pharmacokinetic study in man with single doses of radiolabelled glucosamine by i.v., i.m. or oral route confirmed the analogy of the pharmacokinetic pattern of glucosamine with that found in animals.

The absolute bioavailability in man after a single oral dose of radiolabelled glucosamine was 25% , due to the first-pass effect in the liver in which more than 70% of glucosamine is metabolised. The gastrointestinal absorption is close to 90%, since only 11% of the administered radioactivity is excreted in faeces.

Studies in man were also performed after i. v. or oral administration of unlabelled glucosamine and glucosamine was assayed by ion exchange chromatography in blood and urine. This assay method has a quantitation limit insufficient for sound pharmacokinetic studies. Nevertheless, the results were consistent with those obtained with radiolabelled glucosamine.

5.3 Preclinical safety data

The toxicological studies performed with glucosamine sulfate indicate the large safety margin of the drug.

The following preclinical studies were carried out. The maximum tested doses reported here are those showing no or minimal effects, these were reversible and there was no detectable target organ toxicity:

- acute toxicity studies in mice and rats by i. v. , i.m. and oral route, with up to 5000 mg/kg given by the oral route;
- subchronic toxicity studies of 4 weeks in the rabbit by the i. v. route up to 80 mg/kg, in the rat by the oral route to 240 mg/kg, and in the dog by the i. v. route for 13 weeks up to 300 mg/kg;
- chronic toxicity studies of 52 weeks in the rat with oral doses up to 2700 mg/kg, and of 26 weeks in the dog with oral doses up to 2149 mg/kg;
- embryotoxicity studies in the rat and rabbit by the oral route up to 2500 mg/kg, and fertility studies in the rat by the oral route up to 2149 mg/kg;
- mutagenic potential studies in vitro up to concentration of 5000 $\mu\text{g/ml}$ and in vivo up to the oral dose of 1592 mg/kg in the rat and 7160 mg/kg in the mouse.

The doses used represent a very large multiple of the daily dose currently used in human therapy, which is around 20-25 mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Citric acid (anhydrous) (E330)
Sorbitol (E420)
Macrogol 4000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Over-labelled carton containing overlabelled single dose sachets
Pack size: 20 sachets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

B & S Healthcare Ltd
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Bradfield Road
Ruislip
Middlesex HA4 0NU
United Kingdom

8 Parallel Product Authorisation Number

PPA1328/133/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th February 2010

10 DATE OF REVISION OF THE TEXT