IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0814/001/002
Case No: 2057235

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

Fidia Farmaceutici S.p.A.

Via Ponte della Fabbrica 3/A, **Abano Terme (Padova) 35031**, **Italy**

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

Hyalgan solution for intra-articular injection, 20 mg/2 ml, vial.

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 **01/04/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hyalgan solution for intra-articular injection, 20 mg/2 ml, vial.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg/2 ml of Sodium hyaluronate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for intra-articular injection.
Clear, viscous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the sustained relief of pain in osteoarthritis of the knee.

4.2 Posology and method of administration

Adults (including the elderly)

The contents of one vial (20 mg/2mL) to be injected into the affected joint once a week to a total of five injections, using a standard technique. No adjustment of dose is required in elderly patients.

This can be repeated at not less than 6 monthly intervals.

Children

At present there is not enough evidence to recommend a dosage regimen for use in children.

Intra-articular injection of Hyalgan should be made using precise, anatomical localisation into the joint cavity of the knee to be treated. The injection site in the knee is determined by that location which is easier to reach. Usually a lateral approach can be followed, but in some cases a medial approach is preferable. Strict aseptic precautions should be observed during the administration. The solution in the vial requires only a sterile disposable needle. To ensure sterility the injection site must be carefully cleansed with antiseptic. Care should be taken to expel any trapped air bubbles from the syringe containing Hyalgan prior to administration.

Joint effusion, if present, should be aspirated by arthrocentesis prior to injection of Hyalgan. The arthrocentesis should be made using a 20 gauge needle and the joint should be aspirated to almost dryness, but not to degree that would compromise the accuracy of the subsequent Hyalgan injection. An appropriate examination of the joint fluid present should be carried out to exclude bacterial infection, prior to injection.

The intra-articular injection of Hyalgan can be given using the same needle as used for the arthrocentesis by simply detaching the aspirating syringe and attaching the syringe containing Hyalgan. To make sure the needle is correctly positioned, some synovial fluid should be aspirated prior to the slow injection of Hyalgan. If the patient experiences pain during injection, the procedure may need to be stopped.

For the first 48 hours after the injection, the patient should be advised to rest the treated knee, with as little exercise as possible, avoiding any strenuous or prolonged activity. Subsequently, they may gradually return to their normal level of activity.

Discard any unused Hyalgan.

4.3 Contraindications

Hyalectin, the active ingredient in Hyalgan, is of avian origin. Do not administer to patients with known hypersensitivity to any ingredient of the product or to avian proteins.

Intra-articular injections are contraindicated in cases of infections or skin diseases in the area of the injection site.

4.4 Special warnings and precautions for use

Remove joint effusion, if present, before injecting Hyalgan.

Patients should be carefully examined prior to administration to determine signs of acute inflammation and the physician should evaluate whether Hyalgan treatment should be initiated when objective signs of inflammation are present.

As with any invasive joint procedure, it is recommended that care be taken not to overburden the joint immediately following the intra-articular injection.

Use only if the solution is clear.

See also Section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Since there is limited experience available, Hyalagan should not be administered simultaneously or mixed with other intra-articular injections.

Do not use concomitantly with disinfectants containing quaternary ammonium salts because hyaluronic acid can precipitate in their presence.

4.6 Pregnancy and lactation

No embroytoxicity or teratogenicity has been observed in animal studies. However, there is no experience of the use of Hyalgan in pregnant women and therefore the expected benefit to the mother should be weighed against any potential risk to the foetus.

If Hyalgan is prescribed to a woman of child-bearing potential, she should be advised to contact her physician regarding discontinuance of the product if she intends to become, or suspects that she is, pregnant.

Although it is not expected that Hyalgan would be present in human milk, because many drugs are excreted by this route, caution should be exercised when Hyalgan is administered to a nursing mother and the expected benefit to the mother should be weighed against any potential risk to the neonate.

4.7 Effects on ability to drive and use machines

Hyalgan is not expected to have any effect on the patient’s ability to drive or operate machinery.

4.8 Undesirable effects

Pain, swelling, effusion, heat and redness may rarely occur at the injection site. Such symptoms are usually benign, shortlived, without sequelae and disappear spontaneously within a few days by resting the affected joint and apply ice locally.

Systemic allergic reaction due to individual hypersensivity have been rarely recorded. Isolated cases of an anaphylactic-like reaction have been reported. In post-marketing experience and they had favourable outcomes. No case of anaphylactic-like reactions have been reported during clinical trials.

Allergic – type signs and symptoms such as rash, pruritus and urticaria are also very rare.

In a 495-patient US multicentre placebo- and naproxen- controlled clinical study, the following adverse events occurred with a frequency greater than 5% in the Hyalgan group (versus placebo): headache 18% (17%), rash 7% (9%), ecchymosis 7% (6%) and pruritus 7% (4%). As these events occurred with equal frequency in the placebo group, there is no proven causality in respect of Hyalgan.

4.9 Overdose

Overdosage is unlikely given the route of administration and the single use pack of the drug. No case of overdosage has been reported to date.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hyalgan is a sterile, non-pyrogenic, viscous, aqueous buffered solution of a defined high molecular weight fraction of highly purified hyaluronic acid sodium salt (Hyalectin). Hyaluronic acid is an important component of the body's extracellular matrix and is present in a particularly high concentration in cartilage and synovial fluid. Endogenous hyaluronic acid provides viscosity and elasticity to synovial fluid, which is fundamental for its lubricating and shock absorbing properties, and it is essential for the correct structure of proteoglycans in articular cartilage. In osteoarthritis there is an insufficient amount of, and a change in the quality of, hyaluronic acid in synovial fluid and cartilage. The intra-articular administration of hyaluronic acid into arthritic joints with degenerating cartilage surfaces and pathologically altered synovial fluid improved joint functions.

The observed beneficial effects of exogenous hyaluronic acid may be related to its interactions with various components of the synovial cavity (synoviocytes and chondrocytes).

In controlled clinical studies, treatment cycles with Hyalgan have been shown to ameliorate the symptoms of osteoarthritis for up to 6 months following the end of treatment.

5.2 Pharmacokinetic properties

Sodium Hyaluronate (Hyalectin) administered intra-articularly is eliminated from the synovial fluid within 2 to 3 days. Pharmacokinetic studies have shown that it is quickly distributed to the synovial membrane. The highest concentrations of labelled hyaluronic acid have been detected in the synovial fluid and the articular capsule, followed by, in decreasing order, the synovial membrane, the ligaments and the adjacent muscle.

Hyaluronic acid in synovial fluid has been shown to be not significantly metabolised. Animal studies have shown that some degradation occurs in the tissue surrounding the joints, but the major site for metabolism is the liver and excretion is mainly through the kidneys.

5.3 Preclinical safety data

Hyalectin (Sodium Hyaluronate) was tested in a standard range of toxicological tests, including mutagenicity and reproductive toxicity studies, and produced negative results throughout.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium hydrogen phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Store in the original package.

Do not freeze.

Use immediately once opened.

Discard any unused solution.

6.5 Nature and contents of container

Colourless, Type I borosilicate glass vials with rubber stoppers and aluminium seals containing 2 ml of Hyalgan solution, supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

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

Hyalgan is for intra-articular injection and is supplied as a single-use, ready to use, sterile solution in a 2 ml vial, and must not be diluted. The contents of the vial are sterile and must be used immediately once the container has been opened.

Discard any unused Hyalgan.

7 MARKETING AUTHORISATION HOLDER

Fidia Farmaceutici S.p.A
Via Ponte della Fabbrica 3/A
35031 Abano Terme (Padova)
Italy

8 MARKETING AUTHORISATION NUMBER

PA 0814/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1999

Date of last renewal: 1st April 2009

10 DATE OF REVISION OF THE TEXT

June 2009