Public Assessment Report

UKPAR

Prescription Only to Pharmacy Reclassification

Arthriex 750 mg Film Coated Tablets - PL 36549/0001
Arthriex 1500 mg Film Coated Tablets - PL 36549/0002

CF PHARMA LIMITED

PUBLIC ASSESSMENT REPORT

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1. Introduction

Arthriex tablets (750mg and 1500mg) are indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee as diagnosed by a doctor.

Each Arthriex 750mg Tablets contain 942mg glucosamine sulfate sodium chloride equivalent to 750mg glucosamine sulfate or 589 mg glucosamine. Each Arthriex 1500mg Tablets contain 1884mg glucosamine sulfate sodium chloride equivalent to 1500mg glucosamine sulfate or 1178mg glucosamine.

The Licence holder, CF Pharma Limited applied to make these products available as a Pharmacy (P) medicine for sale without prescription in pharmacies, by or under the supervision of a pharmacist.

The Medicines and Healthcare Products Regulatory Agency (MHRA) considers these products are safe enough to be sold in pharmacies.

2. Background

Osteoarthritis, the most common form of arthritis, is a public health problem throughout the world. Osteoarthritis is a condition in which the natural cushioning between joints -- cartilage -- wears away. When this happens, the bones of the joints rub more closely against one another with less of the shock-absorbing benefits of cartilage.

Glucosamine sulfate, the active ingredient in Arthriex, belongs to a group of medicines called 'other anti-inflammatory and anti-rheumatic agents' as it has a different mode of action compared to painkillers such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. It is found in the body, in the protective cartilage on the ends of the bones and the fluid of the joints. Clinical studies have shown that glucosamine sulfate can be effective in relieving the symptoms of osteoarthritis in the knee joint. The mechanism of action of glucosamine in humans is unknown.

In patients with mild to moderate osteoarthritis, in addition to physical exercise, paracetamol and NSAIDs are the only existing approved medicinal drug alternatives to obtain relief of symptoms such as pain and stiffness. No curative or disease-modifying treatment exists, apart from surgery with arthroplasty.

With the same indication and the same recommended dosage, the glucosamine 750mg and 1500mg tablets are authorised as medicines which can be sold without prescription in 17 other EU countries.

3. Proposed Terms of Reclassification

CF Pharma Limited proposed to make Arthriex 750mg and 1500mg tablets available through Pharmacies with the following proposed terms of reclassification:

- For oral use
- For the relief of symptoms in mild to moderate osteoarthritis of the knee as diagnosed by a doctor in adults aged 18 years and above
- Dose: 1500mg glucosamine sulfate daily, taken as a single dose, or in the case of the 750mg tablets, one tablet twice daily
- Maximum dose: 1500mg
- Maximum daily dose: 1500mg

- Maximum pack size: 135g (3 months' supply: 90 tablets for 1500mg strength and 180 tablets for 750mg strength)

4. Criteria for P classification

To be reclassified from a Prescription Only Medicine (POM) to Pharmacy Medicine (P), a medicine must:

- Be unlikely to be a direct or indirect danger to human health when used without the supervision of a doctor, even if used correctly
- Be generally used correctly (ie not frequently or to a wide extent used incorrectly)
- Not contain substances or preparations of substances where the activity of the product or its side effects require further investigation
- Not normally be prescribed by a doctor for injection (parenteral administration)

These criteria are set out in the Human Medicines Regulations 2012, Regulation 62(3).

5. Assessment of suitability for pharmacy availability

5.1. Prescription Only Criteria

The MHRA assessed the application against the criteria for classification as a Prescription Only Medicine, as stated in section 4.

5.1.1. Direct danger

Direct danger means that a danger may be present if the product causes adverse reactions that are important.

The most common adverse reactions associated with treatment with glucosamine are nausea, abdominal pain, indigestion, constipation and diarrhoea. In addition, headache, tiredness, rash itching, and flushing have been reported. The reported adverse reactions are usually mild and transitory.

Individuals who are considered to be at risk of any detrimental reactions from taking Arthriex tablets will not be given the product unless advised by a doctor. Individuals who are allergic to the active ingredient Glucosamine, sulfates, soya, peanut, shellfish, or any other ingredient of the Arthriex medicine are advised not to take the medicine.

Women who are pregnant or breastfeeding, individuals under the age of 18 years, and those with liver or kidney problems will also not be supplied with Arthriex tablets.

Drug-drug interactions (interactions between Arthriex tablets and other drugs taken at the same time) have been identified, namely the use of warfarin and Arthriex tablets, and the use of oral tetracyclines and Arthriex tablets. However, people known to be taking these medicines will not be supplied with these tablets, and therefore the risk of adverse reactions occurring from potential drug-drug interactions is low.

5.1.2 . Indirect danger

Indirect danger to human health, even when the product is used correctly, could occur where treatment might mask or hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy. Therefore, it is important that the condition or symptoms, for which a

medicinal product not subject to a medical prescription is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision.

Arthriex tablets are indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee as diagnosed by a doctor, and therefore individuals requesting the purchase of these tablets would be aware/familiar of their condition. The patient must speak to their doctor and should not take these tablets if they suffer from other joint diseases such as rheumatoid arthritis. This information is clearly communicated in the Patient Information Leaflet (PIL) and on the carton. The patient is also instructed via the PIL that if no relief of symptoms is experienced after 2-3 months, medical advice should be sought.

Appropriate training material (A Pharmacist Guide to Dispensing Arthriex) is provided to pharmacists and pharmacy staff to aid in the suitable provision of these tablets. The outer carton also displays an image of the knee, and the indication of 'osteoarthritis of the knee' has been highlighted to further inform pharmacists and patients on the indication of this product.

5.1.3 . Incorrect use – frequently and to a very wide extent

The risk of incorrect use or the tablets being used off-label is minimised by the fact that the patient is under supervision by both pharmacist and by the doctor prior to starting treatment with this product.

There is no reported misuse, abuse, dependency, or overdose associated with glucosamine, therefore the incorrect use of Arthriex tablets is expected to be low.

5.1.4. Activity and/or adverse reactions require further investigation

The proposed tablets do not contain substances or preparations, the activity and/or adverse reactions of which require further investigation. In case of glucosamine compounds, the only adverse effect that cannot be foreseen is allergy, and this is not related to quantity of ingestion.

5.1.5. Is normally prescribed as an injection

This product is administered orally, so this does not apply.

5.2 Risk Management Plan

The application included a risk management plan (RMP). RMPs are documents that contain information on a medicine's safety profile and one or more of the following:

- How any risks identified in the safety profile will be prevented or minimised in patients.
- Plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine.
- Risk factors for side effects.
- Measuring the effectiveness of measures taken to prevent or minimise risks.

The RMP for this product identified the main risks associated with the product and proposed how these will be managed in the product information (Summary of Product Characteristics, labelling and Patient Information Leaflet) and by the provision of training material for pharmacists and their staff.

5.2.1. Training resources

A Pharmacist Guide to Dispensing Arthriex was developed to aid pharmacists and pharmacy staff in the dispensing of Arthriex. The Pharmacist Guide is a Tri-fold brochure and contains the following information:

- Brief background on osteoarthritis of the knee
- An Introduction to Arthriex
- Details of who the product is not suitable for
- Details of which patients should speak to the doctor first before taking the medicine
- Contact details
- A reminder to report adverse reactions

The Royal Pharmaceutical Society was also contacted with regards to reviewing the educational brochure as part of this reclassification from POM status to P status in the UK.

6. Advice from the Commission on Human Medicines (CHM)[1]

The Commission considered whether Glucosamine sulfate 750mg and 1500mg Film-coated Tablets containing gluosamine sulfate falls within a description or class specified in regulation 62(3) of the Human Medicines Regulations 2012, and advised in favour of non-prescription availability as a Pharmacy medicine, under the following conditions:

- for the relief of symptoms in mild to moderate osteoarthritis of the knee as diagnosed by a doctor
- maximum dose 1500mg
- maximum daily dose 1500mg
- maximum pack size 135g.

It was suggested by the Commission that the pack size should be reduced to 45g (1 month supply), unless otherwise justified by the applicant.

The applicant's response included evidence to support long term use which indicated that the optimal short term treatment period is 3 months, which was considered to be satisfactory.

7. Consultation on Pharmacy Availability of Arthriex Tablets

Consultation document ARM[2] 96, which summarises the proposals on the POM to P reclassification of Glucosamine sulfate 750mg and 1500mg Film Coated Tablets, was posted on the GOV.UK website on 14 July 2017. The deadline for comments was given as 4 August 2017. ARM 96 can be accessed via the following link:

https://www.gov.uk/government/consultations/proposal-to-make-arthriex-750mg-and-1500mg-film-coated-tablets-available-from-pharmacies

8. Responses to consultation ARM 96

There were 7 responses received, 6 were in favour of the reclassification, 1 was not in favour. 1 response requested that their response remain confidential.

Of the 6 responses in favour, one was from an individual who was a regulatory affairs consultant. The other 5 responses in favour were from organisations: The Royal College of Physicians, The Royal Pharmaceutical Society, The National Pharmacy Association, the Guild of Healthcare

[1] The Commission on Human Medicines (CHM) is an advisory non-departmental public body, sponsored by the Department of Health that advises ministers on the safety, efficacy, and quality of medicinal products.
[2] ARM Stands for Application to Reclassify a Medicine. An ARM consultation is a public consultation inviting views from all stakeholders on a proposal to reclassify a medicine from a Prescription Only Medicine (POM) to Pharmacy Medicine (P), or from a Pharmacy Medicine (P) to one on the General Sale List (GSL).

Pharmacists, and a respondent who requested that their response remain confidential. The 1 response not in favour of the reclassification was from an organisation; the British Society for Rheumatology's Osteoarthritis Special Interest Group.

The responses provided did not raise any new safety concerns with respect to the reclassification of Arthriex 750mg and Arthriex 1500mg Film Coated Tablets as a Pharmacy (P) medicine.

Comment about the Summary of Product Characteristics (SmPC)[3]
One respondent suggested it was not necessary to have section 4.4 of the SmPC detail what should be stated on the product label.

These details are an important way of managing the risk of reclassifying this product. It allows healthcare professionals to be aware of what information has been made available to the patient on the label and sets out the labelling conditions that are a requirement for any glucosamine products that are classified as P in the future.

Comment about the efficacy of glucosamine
One respondent questioned the evidence for the efficacy of glucosamine in osteoarthritis. The efficacy of glucosamine for the relief of symptoms of mild to moderate osteoarthritis of the knee was considered by the CHM when the product was first licensed. Clinical trial data supports the effectiveness of the product for the relief of symptoms of mild to moderate osteoarthritis of the knee.

Comments about the proposed Patient Information Leaflet (PIL)
All the other responses received had comments suggesting changes to the proposed PIL. As a result, the following changes were made to the leaflet:

Section 1: What the medicine is and what it is used for

- The sentence about Glucosamine not being indicated for the treatment of acute painful symptoms in section 4.1 and 4.2 of the SmPC of the product should be included in Section 1 of the PIL as follows: "This medicine should only be used for the relief of symptoms (signs of illness) of mild to moderate osteoarthritis of the knee that has previously been diagnosed by your doctor. Glucosamine is not indicated for the treatment of acute painful symptoms. Please make sure that you have been diagnosed with osteoarthritis of the knee before taking this product."
- The message about not treating any other types of arthritis should be clearly emphasised in section 1 of the PIL: "This medicine is to be used only for the treatment of mild to moderate osteoarthritis of the knee. This medicine is not to be used for the treatment of any other areas of your body affected by Osteoarthritis or to treat other types of arthritis e.g. rheumatoid arthritis."
  Thus, the following sentence would be deleted: "This medicine is not to be used for treating rheumatoid arthritis".

Section 2: What you need to know before you take the medicine

- Under the 'Warnings and Precautions' section of section 2 of the PIL, the following statement ('You must talk to a doctor if you intend to use this medicine for a very long time because there is not enough information available on the use of Glucosamine beyond 3 years') should be replaced with "If you experience a benefit from taking this medicine and intend to continue using it for over 3 months, please discuss this with your doctor."

Section 3: How to take the medicine

- Similar to in Section 1, the sentence about Glucosamine not being indicated for the treatment of acute painful symptoms in section 4.2 of the SmPC of the product should be included in Section 3 as follows: "One tablet should be taken twice daily or two tablets to be taken once

[3]SmPC stands for Summary of Product Characteristics. The SmPC is a legal document describing a medicine's properties and how it can be used. SmPCs are available online via the MHRA.

daily. The tablets should be swallowed whole with water. Glucosamine is not indicated for the treatment of acute painful symptoms."

- In Section 3, the following sentence should replace the word 'stop' with 'continue', as the word 'stop' implies that the patient might continue with the treatment: "If you do not feel any better after 2-3 months, you should speak to your doctor, pharmacist or nurse to find out if you should stop continue taking this medicine."

Section 4: Possible side effects of the medicine

- Section 4 of the PIL should be amended to give more appropriate advice if a patient experiences certain side effects leading to an emergency situation, i.e. "You should stop taking Arthriex 750 mg Film Coated Tablets and see your doctor immediately or go to the casualty department at your nearest hospital if you experience signs of illness such as: swollen face, tongue and/or pharynx and/or difficulty to swallow or hives together with difficulties to breathe (angioedema)."

It was considered that some comments received did not require changes to be made to the PIL. These are listed below and the reasons they did not need to be acted upon are given in sub-bullets below them.

- The sentence in section 2 of the PIL (You must talk to a doctor if you do not feel better or if you feel worse after 2-3 months) has the potential to be misread and could benefit from rewording.
    - This wording is included in the guidance (QRD template) for the PIL that allows a certain degree of consistency across leaflets. It is considered adequate to retain this sentence.

- If a patient is on medication for high cholesterol, they should consult their GP prior to taking this medicine, so it should be considered to add this to the 'warnings and precautions' section of the PIL.
    - The information in section 4.4 of the SmPC has been correctly transferred into the 'warnings and precautions' section of the PIL, which states that "high cholesterol (hypercholesterolemia) has been observed in a few cases in patients treated with Glucosamine sulfate tablets", and also recommends monitoring of cholesterol levels. This is considered adequate.

- The stability information in section 5 should be reviewed regarding the use of the tablets after opening the container.
    - The leaflet reflects the information in the marketing authorisation. This information is supported by suitable stability data, and is therefore clearly communicated to the patient in the leaflet.

- The information in section 4.4 of the SmPC referring to what the label will state may not be necessary information
    - This information in section 4.4 allows healthcare professionals to be aware of what information is available to the patient on the label.

- The leaflet states that the medicine can only be used where mild to moderate osteoarthritis of the knee has been previously diagnosed by a doctor, this will not always be the case as the medicine will be promoted for sale or certainly could be, it would be better if the leaflet stated that the patient has the symptoms of osteoarthritis.
    - Stating that the medicine can be used where the patient has symptoms of osteoarthritis could be an indirect danger to health, as the symptoms may be similar to that of other serious conditions such as rheumatoid arthritis, systemic lupus, gout and tumours. By using this medicinal product in these conditions, it could delay patients in getting medical treatment for a more serious condition. The Commission has also advised in

favour of the indication where it is stated that the osteoarthritis of the knee must be previously diagnosed by the doctor. Therefore, this information in the leaflet is consistent with the marketing authorisation.

- The leaflet also stated that if you don't feel better or feel worse in 2 to 3 months you need to go back to your doctor. However, it also states that it may take several weeks or longer to obtain benefit from taking the medicine. This is contradictory.
    - Both statements may appear as being contradictory, however they are both essential in the leaflet. By informing the patient of the length of time it may take to experience any benefit from the tablets, it encourages them to continue and not expect immediate effects. The statement about seeking medical advice if the patient does not feel better or if they feel worse is also necessary as it could determine whether the tablets should be continued or if another treatment is required. If this statement was not present, the patient could continue without being aware of an underlying cause which could require further treatment.

- The leaflet states that it can only be used where one joint is affected, with osteoarthritis it is highly likely that both joints are affected, as such any Pharmacist would need to intervene to prevent supply where both knees are affected
    - The warning is in line with the marketing authorisation, and the training for pharmacists also advises the referral to the doctor if there is pain in more than one joint. Therefore, as also agreed by the Commission, the indication of this will be for the relief of symptoms in mild to moderate osteoarthritis of the knee as diagnosed by a doctor.

- The addition of informing a pharmacist as well as a doctor should be included in the PIL if the patient does not feel better or feels worse, and also if the patient takes large quantities of Glucosamine.
    - In both of the above situations, the doctor may be able to make an informed decision about whether the patient should continue taking the medicine, but could also provide immediate medical attention if the patient has taken large quantities. However, as there is training material being provided to pharmacists, the signposting of patients to a pharmacist would be a useful source of information, and would aid in building a rapport between the pharmacist and patient to further strengthen the reclassification of this product. Section 3 of the PIL already states "If you do not feel any better after 2-3 months, you should speak to your doctor, pharmacist or nurse…", and the end of this section also mentions 'If you have any further questions on the use of this product, ask your doctor or pharmacist.' This is considered adequate to help identify the pharmacist as a source of information or advice.

- Section 5 of the PIL should replace 'Ask your pharmacist how to throw away medicines you no longer use' with 'Return any medicines you no longer use to the pharmacist'.
    - In line with the guidance, this is standard wording, and should remain as 'Ask your pharmacist how to throw away medicines you no longer use'. This advice encourages the patient to always speak to their pharmacists about the best method of disposal.

9. Conclusion

Assessment of the responses to consultation on the application for Arthriex 750 mg Film Coated Tablets - PL 36549/0001 and Arthriex 1500 mg Film Coated Tablets - PL 36549/0002 has revealed no new issues of concern in addition to those considered by the Commission on Human Medicines and on which it was reassured. Considering the advice from Commission, the Licensing Authority has taken the decision to approve Pharmacy legal status for Arthriex 750mg Tablets and Arthriex 1500mg Tablets.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC and PIL for Arthriex 750mg Tablets and Arthriex 1500mg Tablets, classified as P, are available on the MHRA website.

The approved labelling for Arthriex 750mg Tablets and Arthriex 1500mg Tablets is presented below.

Medicines and Healthcare products Regulatory Agency,
September 2017