Public Assessment Report

Decentralised Procedure

YOINTY 625 MG HARD CAPSULES

GLUCOSAMINE HYDROCHLORIDE

UK/H/3497/001/DC
UK Licence No: PL 05517/0001

BIOIBERICA SA
On 28th February 2012, the UK granted Bioiberica S.A. a Marketing Authorisation (licence) for Yointy 625 mg hard capsules.

Yointy 625 mg hard capsules belong to the group of medicines called other antiinflammatory and anti-rheumatic agents, non-steroids.

Yointy 625 mg hard capsules contain the active ingredient glucosamine hydrochloride.

Yointy 625 mg hard capsules are used to relieve the symptoms in mild to moderate osteoarthritis of the knee.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Yointy 625 mg hard capsules outweigh the risks and a Marketing Authorisation was granted.
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# Module 1

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| **MA Holder** | Bioiberica S.A.  
Ctra. Nacional II, Km. 680,6  
08389 Palafolls (Barcelona)  
Spain |
| **Reference Member State (RMS)** | The United Kingdom (UK) |
| **Concerned Member States (CMS)** | Bulgaria (BG), the Czech Republic (CZ), Spain (ES), Hungary (HU), Iceland (IS), Portugal (PT), Romania (RO) and Sweden (SE) |
| **Procedure Number** | UK/H/3497/001/DC |
| **End of Procedure** | Day 210: 18th January 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Yointy 625 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 625 mg of glucosamine (equivalent to 750 mg of glucosamine hydrochloride).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard.
Brown coloured hard gelatine capsules of size n°0EL.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Relief of symptoms in mild to moderate osteoarthritis of the knee.

4.2 Posology and method of administration
Adults (including the elderly):
The recommended dose is 2 capsules to be taken once a day (1,250 mg/day glucosamine).

Glucosamine is not indicated for the treatment of acute pain. The relief of the pain may occur after
several weeks of treatment, and sometimes after a longer time. If no relief of pain occurs after 2-3
months, the continuation of the treatment should be re-evaluated.

Paediatric population:
Yointy is not recommended for use in children below 18 years of age, due to a lack of data on safety
and efficacy.

Impaired liver and/or renal function:
In patients with impaired renal and/or liver function no dose recommendations can be given, since no
studies have been performed.

Method of administration:
The capsules can be taken before, during or after meals.
The capsules should be swallowed whole without chewing, and with a sufficient amount of water.

4.3 Contraindications
Known hypersensitivity to glucosamine or to any of the excipients.

Yointy must not be given to patients who are allergic to shellfish as the active substance is obtained
from shellfish.

4.4 Special warnings and precautions for use
A doctor should be consulted to rule out the presence of joint disease for which other treatment should
be considered.

In patients with impaired glucose tolerance, monitoring of the blood glucose levels and, where relevant,
insulin requirements is recommended before start of treatment and periodically during treatment.

In patients with known risk factor for cardiovascular disease, monitoring of the blood lipid levels is
recommended, since hypercholesterolemia has been reported in a few cases in patients treated with
glucosamine.

A report on exacerbated asthma symptoms triggered after initiation of glucosamine therapy has been
described (symptoms resolved after withdrawal of glucosamine). Asthmatic patients starting on
glucosamine should therefore be aware of potential worsening of asthma symptoms.
4.5 Interaction with other medicinal products and other forms of interaction
Increased effect of coumarin anticoagulants (e.g. warfarin) during concomitant treatment with glucosamine has been reported. Patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy.

Concurrent treatment with glucosamine may increase the absorption and serum concentrations of tetracyclines, but the clinical relevance of this interaction is probably limited. Due to limited documentation on potential drug interactions with glucosamine, one should generally be aware of altered response or concentration of concurrently used medical products.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no adequate data from the use of glucosamine in pregnant women. From animal studies only insufficient data are available. Glucosamine should not be used during pregnancy.

Breast Feeding
There are no data available on the excretion of glucosamine in human milk. The use of glucosamine during breastfeeding is therefore not recommended as there are no data on the safety of the newborn.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. If dizziness or drowsiness is experienced, car driving and the operating of machinery are not recommended.

4.8 Undesirable effects
The most common adverse reactions associated with treatment with glucosamine are described below with the frequencies “common” (defined as ≥1/100 to <1/10), “uncommon” (defined as ≥1/1,000 to ≤1/100) and “not known” (defined as cannot be estimated from the available data) and are listed by body system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The reported adverse reactions are usually mild and transitory.

Nervous system disorders
Common: Headache, tiredness.
Not known: Dizziness

Respiratory, thoracic and mediastinal disorders
Not known: Asthma / asthma aggravated

Gastrointestinal disorders
Common: Nausea, abdominal pain, indigestion, diarrhoea, constipation.
Not known: Vomiting.

Skin and subcutaneous tissue disorders
Uncommon: Rash, itching, flushing.
Not known: Angioedema, urticaria.

Metabolism and nutrition disorders
Not known: Diabetes mellitus inadequate control, hypercholesterolaemia.

General disorders and administration site conditions
Not known: Oedema / peripheral oedema.

4.9 Overdose
No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antiinflammatory and antirheumatic agents, non-steroids. ATC Code: M01AX05

Glucosamine is an endogenous substance, a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. In vitro and in vivo studies have shown
glucosamine stimulates the synthesis of physiological glycosaminoglycans and proteoglycans by chondrocytes and of hyaluronic acid by synoviocytes.

The mechanism of action of glucosamine is unknown. The period to onset of response cannot be assessed.

5.2 Pharmacokinetic properties
Glucosamine is a relatively small molecule (molecular mass 179), which is easily dissolved in water and soluble in hydrophilic organic solvents.

The available information on the pharmacokinetics of glucosamine is limited. The absolute bioavailability is unknown. The distribution volume is approximately 5 litres and the half-life after intravenous administration is approximately 2 hours. Approximately 38% of an intravenous dose is excreted unchanged in the urine.

The ADME (absorption, distribution, metabolism and excretion) profile for glucosamine in man has not been completely elucidated.

5.3 Preclinical safety data
Non-clinical data from glucosamine reveal no special hazard for humans based on studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Magnesium stearate.
Capsule composition:
Gelatin
Red iron oxide (E172)
Titanium dioxide (E171)
Black iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
PVC/PVDC/aluminium blister packed in cardboard carton.
Pack-sizes of 60 hard capsules (6 blisters of ten capsules each) and 180 hard capsules (3 packs of 60 hard capsules).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
BIOIBERICA S.A.
Ctra. Nacional II, Km. 680,6
08389 Palafolls (Barcelona)
Spain.

8 MARKETING AUTHORISATION NUMBER(S)
PL 05517/0001
9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
    28/02/2012

10  DATE OF REVISION OF THE TEXT
    28/02/2012
Module 3
Patient Information Leaflet

Please note that there is no mock-up available. The marketing authorisation holder has stated that it does not intend to market the product; therefore no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL to the regulatory authority for review before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Yointy 625 mg hard capsules

Glucosamine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Yointy 625 mg hard capsules is and what it is used for
2. Before you take Yointy 625 mg hard capsules
3. How to take Yointy 625 mg hard capsules
4. Possible side effects
5. How to store Yointy 625 mg hard capsules
6. Further information

The name of this medicine is Yointy 625 mg hard capsules. However the product will be referred to as Yointy within the text of the leaflet.

1. WHAT Yointy IS AND WHAT IT IS USED FOR

Yointy belongs to the group of medicines called other anti-inflammatory and anti-rheumatic agents, non-steroids.
Yointy is used to relieve the symptoms in mild to moderate osteoarthritis of the knee.

2. BEFORE YOU TAKE Yointy

Do not take Yointy
- if you are allergic (hypersensitive) to glucosamine or to any of the other ingredients of Yointy.
- if you are allergic (hypersensitive) to shellfish, as glucosamine is obtained from shellfish.

Take special care with Yointy
- if your suffer from diabetes mellitus or impaired glucose tolerance. More frequent controls of your blood glucose levels may be necessary when starting treatment with Yointy.
- if you have a known risk factor for cardiovascular disease (e.g. hypertension, diabetes mellitus, raised cholesterol or if you smoke). It is recommended to control your cholesterol before starting treatment with Yointy, since raised cholesterol has been observed in a few cases in patients treated with glucosamine.
- if you suffer from asthma. When starting on glucosamine, you should be aware of potential worsening of symptoms.
- if you have impaired kidney or liver function, since no studies with glucosamine have been performed in this patient group.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
It is particularly important to tell your doctor or pharmacist if you are taking any of the following medicines:
- tetracyclines (antibacterials used against infection).
- warfarin or similar type of products (anticoagulants used to prevent blood-clotting). The effect of the anticoagulant may be increased in association with glucosamine. Patients treated with such combinations should therefore be monitored extra carefully when initiating or ending glucosamine therapy.

**Taking Yointy with food and drink**
Yointy could be taken before, during or after a meal.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.
Yointy should not be used during pregnancy.
The use of Yointy is not recommended during breastfeeding.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed. If you experience dizziness or drowsiness from the capsules, you should not drive or operate machinery.

3. **HOW TO TAKE Yointy**
Always take Yointy exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is 2 capsules once daily (1250 mg glucosamine).

Swallow the hard capsules together with some water or other suitable liquid. Do not chew the capsules.

**Use in children**
Yointy is not recommended for the use in children below 18 years.

Glucosamine is not indicated for the treatment of acute pain. Relief of symptoms (especially pain relief) may not happen for several weeks and sometimes longer. If there is no benefit after 2-3 months, please tell your doctor.

**If you take more Yointy than you should**
If you have taken too many Yointy capsules you must contact your doctor or nearest hospital.

**If you forget to take Yointy**
Do not take a double dose to make up for a forgotten dose. If it is almost time for your next dose, skip the forgotten dose and carry on taking Yointy as scheduled.

**If you stop taking Yointy**
Your symptoms may reoccur.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**
Like all medicines, Yointy can cause side effects, although not everybody gets them. These are usually mild and transient.

The following side effects have been reported:
PAR Yointy 625 mg Hard Capsules

**Common** (occur in less than 1 in 10 but more than 1 in 100 patients):
Headache, tiredness, feeling sick, abdominal pain, indigestion, diarrhoea, constipation.

**Uncommon** (occur in less than 1 in 100 but more than 1 in 1000 patients):
Rash, itching, flushing

**Frequency not known** (can not be estimated from available data)
Vomiting, urticaria, dizziness, swelling of the feet or ankles, angioedema. Aggravation of pre-existing asthma, blood glucose control worsened in diabetic patients.

Elevated cholesterol levels have been also reported. It is not possible to determine whether these events were directly related to glucosamine.

If any of the side effects get serious or worsen, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE Yointy**

Keep out of the reach and sight of children.

Do not store above 30°C. Store in the original package to protect from moisture.

Do not use Yointy after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Yointy contains**
- The active substance is glucosamine. Each capsule contains 625 mg of glucosamine (equivalent to 750 mg of glucosamine hydrochloride).
- The other ingredient is magnesium stearate.

*Capsule composition: gelatin, red iron oxide (E172), titanium dioxide (E171), black iron oxide (E172).*

**What Yointy looks like and contents of the pack**

Yointy are brown coloured hard gelatine capsules. Yointy is delivered in a cardboard box containing 60 and 180 capsules in blister packs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
BIOIBERICA S.A.,
Ctra. Nacional II, Km. 680,6
08389 Palafrugell (Barcelona)
Spain.

**Manufacturer**
JURIACH&Cia, S.A. Av. Camí Reial 51-57
08184 Palau Solità i Plegamans (Barcelona)

**This leaflet was last approved in:** 01/2012

Detailed information on this medicine is available on the web site of MHRA [http://www.mhra.gov.uk](http://www.mhra.gov.uk)
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Bulgaria, the Czech Republic, Spain, Hungary, Iceland, Portugal, Romania, Sweden and the UK considered that the application for Yointy 625 mg hard capsules could be approved. This Prescription Only Medicine (POM) is indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee.

This application for Yointy 625 mg hard capsules was submitted according to Article 10.a of Directive 2001/83/EC; a ‘well established use’ application.

Formed in the body from glucose, glucosamine is one of the principal substrates in the biosynthesis of numerous important sugar-based compounds such as glycosaminoglycans, which form most of the cartilage tissue, proteoglycans, glycoproteins, and glycolipids. Glucosamine is structurally incorporated into bones, cartilage, tendons, and ligaments. It helps to generate and maintain the thickness and elasticity of synovial fluid in joints and vertebrae. The biosynthesis of glucosamine declines with age. It is widely used in the treatment of degenerative rheumatic disorders such as osteoarthritis.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance.

No clinical studies have been performed and none are required for this application because the pharmacology of glucosamine hydrochloride is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan (RMP) has been submitted. Any additional safety concerns were not considered a specific safety risk. The RMP concluded that except for routine pharmacovigilance measures, no additional risk minimisation activities are considered necessary.
II. ABOUT THE PRODUCT

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<th>Name of the product in the Reference Member State</th>
<th>Yointy 625 mg hard capsules</th>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antiinflammatory and antirheumatic agents, non-steroids (M01AX05)</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<td>Reference Member State</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Bioiberica S.A. Ctra. Nacional II, Km. 680,6 08389 Palafolls (Barcelona) Spain</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN name: Glucosamine hydrochloride
Chemical name: 2-amino-2-deoxy-β-D-glucopyranose hydrochloride

Structural formula:

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\begin{center}
\includegraphics[width=0.3\textwidth]{structural_formula.png}
\end{center}
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Molecular formula: C₆H₁₃NO₅.HCl

Appearance: White to almost-white crystalline powder.

Molecular weight: 215.6 g/mol
Solubility: Freely soluble in water, slightly soluble in methanol and practically insoluble in acetone and ethanol.

The source of glucosamine hydrochloride used in the product complies with a satisfactory in-house specification.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate specification with suitable test methods and limits is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidance.

Stability studies have been performed with the active substance and no significant changes were observed. On the basis of the results, a suitable re-test period could be approved.
Other ingredients in the capsules consist of the pharmaceutical excipients magnesium stearate, gelatin, red iron oxide (E172), titanium dioxide (E171) and black iron oxide (E172).

With the exception of black iron oxide (E172) and red iron oxide (E172), all excipients comply with their respective European Pharmacopoeia monographs. Red iron oxide (E172) and black iron oxide (E172) comply with the EC directive 95/45/EC. Red iron oxide also complies with the National Formulary.

With the exception of gelatin, none of the excipients used contain material of animal or human origin. A confirmation has been provided that the magnesium stearate used in this product is of vegetable origin. Valid transmissible spongiform encephalopathy (TSE) Certificates of Suitability (CEP) have been provided for gelatin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to evaluate the viability of a capsule formulation containing 750 mg glucosamine hydrochloride (corresponding to 625 mg glucosamine) with the proposed excipients.

The applicant has provided suitable product development information. Valid justification for the use and amount of each excipient has been provided.

**Manufacturing Process**

Satisfactory batch formulae for each batch size have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. A commitment has been provided to perform process validation for the first three commercial-scale batches of the drug product.

**Finished Product Specification**

The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

This product is packaged in blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVdC) and aluminium.

Pack sizes are:
- 60 hard capsules (6 blisters of 10 capsules)
- 180 hard capsules (3 packs of 60 hard capsules)

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directive regarding contact with food.
Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 36 months with the following storage instructions:
‘Do not store above 30°C. Store in the original package in order to protect from moisture.’

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically acceptable. A representative sample of the UK SmPC, PIL text and label mock-up are included in modules 2, 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of glucosamine hydrochloride are well-known. As glucosamine hydrochloride is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3  CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required. An overview based on literature review is therefore appropriate.

Pharmacokinetics
Data from the literature regarding the pharmacokinetics of glucosamine in man have been provided.

In a study by Persiani et al (2005), in 12 healthy volunteers, glucosamine sulphate (GS) was found to be rapidly absorbed after oral administration, with linear pharmacokinetics in the range 750 – 1500 mg. Time of maximum plasma concentration (Tmax) occurred at 3-4 hours. Elimination half-life was estimated at 15 hours. The study is supportive of once daily dosing.

In a study by Setnikar et al (1993), six healthy male volunteers received radio-labelled GS, by the oral, intramuscular (i.m.) or intravenous (i.v.) route. The area under curve (AUC) following oral administration was 26 % of that following parenteral administration, indicating significant first pass metabolism following absorption from the gastro-intestinal tract.

Anderson et al (2005) carried out a meta-analysis of the literature on absorption, distribution, metabolism and elimination. It has been shown that glucosamine sulphate or hydrochloride dissociates to free glucosamine in the stomach. Around 90 % is absorbed in the small intestine. The authors also conclude, based on a relatively low affinity for glucose transporter proteins, that glucosamine at therapeutic dose would not be expected to have a discernable effect on metabolic pathways involved in glucose metabolism in humans.

A review by Matheson and Perry (2003) includes an analysis of absorption, distribution, metabolism and excretion (ADME) studies. Glucosamine binds to plasma globulins and rapidly diffuses from plasma into most tissues and organs. Glucosamine is metabolised by the liver. The authors state that although no formal drug interaction studies were performed, the approved labelling of at least one glucosamine-containing medicinal product includes the warning that oral glucosamine can enhance the absorption of concomitantly administered tetracyclines and decrease that of penicillin or cloramphenicol.

Pharmacokinetic conclusion
The pharmacokinetic data submitted from the literature are acceptable. There are no data from formal interaction studies, or pharmacokinetics in special patient groups. This is adequately reflected in the SmPC.

Pharmacodynamics
References to describe the pharmacodynamics of glucosamine have been provided. Five studies are reported (Bassleer et al 1992; Derfoul et al 2007; Dodge et al 2003; Largo et al 2003 and Piperno et al 2000). These were in vitro studies in which glucosamine was added to chondrocytes isolated from human normal and osteoarthritic articular cartilage. The results of the studies suggest that glucosamine may have a chondroprotective mechanism of action in vivo. However the mechanism of action relevant to symptom modification and structure modification in human osteoarthritis (OA) remains unknown.

Pharmacokinetic conclusion
The pharmacodynamic data submitted from the literature are acceptable.
Efficacy
A description of available clinical efficacy studies is provided in the clinical overview and summary of clinical efficacy.

According to the *Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis* (CPMP/EWP/784/97 Rev.1), maintenance of improvement should be evaluated after at least 3 months, when considering modification of symptoms. In addition it is recommended that only one joint should be investigated as the target joint per study. Taking these factors into account, along with the relevance of the inclusion criteria and studied regimen to the proposed indication and posology, six studies are selected for a more detailed summary below:

**Cibere et al 2004**
This was a double-blind, randomised, placebo-controlled trial investigating the efficacy of glucosamine sulphate (GS) in knee OsteoArthritis (OA). One hundred and thirty-seven patients who had experienced at least moderate improvement in knee pain after starting to use GS were randomised to maximum 1500 mg GS (equivalent to the dose taken prior to start of study) or placebo daily for 6 months or until disease flare, whichever occurred first. The primary outcome was the proportion of disease flares in each treatment arm, using intent to treat (ITT) analysis. Secondary outcomes included time to disease flare; analgesic medication use; severity of disease flare and change in pain, stiffness, function and quality of life. Disease flare was seen in 42 % of placebo patients and 45 % of glucosamine patients ($P=0.76$). In the Cox regression analysis, after adjustment for sex, study site and OA radiographic severity, time to disease flare was not significantly different in the GS compared with placebo group. No differences were found in severity of disease flare or other secondary outcomes between placebo and GS patients.

**Clegg et al (2006)**
The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was a multi-centre, double blind, placebo- and active-controlled study in which 1583 patients with symptomatic knee OA were randomly assigned to four different treatment arms. For 24 weeks, 317 patients were assigned to receive 1500 mg of glucosamine hydrochloride (GH) daily. The other treatment arms included 1200 mg of chondroitin sulphate daily, both GH and chondroitin sulphate daily, 200 mg of celecoxib daily or placebo. Up to 4000 mg acetaminophen (paracetamol) was allowed as rescue analgesia. Assignment was stratified according to the severity of knee pain. The primary outcome measure was a 20 % decrease in knee pain from baseline to week 24 (WOMAC pain sub-scale). Secondary outcome measures included scores for the WOMAC stiffness and function subscales, patients global assessment of disease status and response to therapy, the investigator’s global assessment of disease status and response to therapy, soft tissue swelling and/or effusion in the index knee, scores on the SF-36 quality of life questionnaire, scores on the health assessment questionnaire and the use of rescue analgesia. Overall GH was not found to be significantly better than placebo in reducing knee pain by 20 %.

**Hughes et al (2002)**
This was a randomised, placebo-controlled, double-blind trial to investigate the efficacy of GS in OA of the knee. Eighty patients with OA of the knee were randomised to receive either 500 mg of GS three times daily or placebo for 6 months. Patients were assessed four times during the study period at 0, 6, 12, and 24 weeks. The primary outcome measure was the visual analogue scale (VAS) overall assessment of pain in the affected knee. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate the functional activity and the McGill pain questionnaire assessed the effective and sensory components of pain. Osteoarthritis Research Society International (OARSI) response criteria
for relative and absolute reduction on pain and disability were used to classify the patients. Patients could be classified as responders in two ways: if their percentage reduction in global pain VAS was greater than 45 % and there was a minimum absolute reduction of 20 mm, or if their percentage reduction in global pain VAS was less than 45 % but greater than 15 % and there was a minimum absolute reduction of 10 mm, and the WOMAC function score was greater than 30 %.

There were no statistically significant differences in the primary outcome between groups at any time point during the study.

**McAlindon et al (2004)**

This study was a 12-week, double-blind, randomised, placebo-controlled study of glucosamine in knee OA. Via the internet, 205 subjects aged 45 and over were recruited and their medical records were reviewed to confirm eligibility, i.e. at least one knee meeting American College of Rheumatology (ACR) criteria for knee OA. Patients were randomly assigned to receive either 1500 mg glucosamine (GS or GH) daily (n=101) or placebo (n=104); of these 93 in each arm completed the study. The primary efficacy outcome was the WOMAC pain subscale. Additional outcomes were the WOMAC physical function and stiffness score, the overall WOMAC score and analgesic use. All treatment effects were self-assessed and patients were not seen in person by an Investigator at any point during the study. There was no difference between treatment groups in terms of change in pain score, stiffness, physical function, overall score and analgesic use.

**Pavelka et al (2002)**

The aim of this double-blind, randomised, placebo-controlled trial was to determine whether 3 years of treatment with glucosamine can modify the progression of joint structure and symptom changes in knee OA. Using ACR criteria, 202 patients were randomised to receive either GS (1500 mg daily) or placebo. Changes in radiographic minimum joint space width (JSW) were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using Lequesne’s Index of Severity of the Knee (ISK) and WOMAC. OA was of mild to moderate severity at enrolment, with average JSWs of slightly less than 4 mm and a Lequesne’s ISK score of less than 9 points. Progressive joint space narrowing with GS was (0.04 mm; 95% CI, -0.06 to 0.14) compared to -0.19 mm on placebo (95% CI, -0.29 to 0.09) after 3 years, with a significant difference between groups (P=0.001). Fewer patients treated with GS experienced predefined severe narrowing (>0.5 mm): 5 % vs. 14 % (p=0.05). There were significant final differences in favour of GH for the Lequesne’s ISK score (GS -1.7; PL -0.82, P=0.002) and the WOMAC total index (GS -8.0; PL -4.9, P=0.01).

**Reginster et al (2001)**

This randomised, double-blind placebo-controlled study assessed the effects of GS on the long-term progression of knee OA joint structure changes and symptoms. Using ACR criteria, 212 patients were recruited and received either 1500 mg GS daily or placebo for 3 years. Weight bearing, anteroposterior radiographs of each knee in full extension were taken at enrolment and after 1 and 3 years. Mean JSW of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum JSW, i.e. at the narrowest point, was measured by visual inspection with a magnifying lens. OA symptoms were assessed by the WOMAC OA index.

The 106 patients on placebo had progressive joint space narrowing, with a mean joint space loss after 3 years of -0.31 mm (95 % CI -0.48 to -0.13). There was no significant loss of joint space in the 106 patients treated with GS: -0.06mm (-0.22 to 0.09). As assessed by change in WOMAC scores over the 3 years treatment duration, symptoms worsened slightly in patients on placebo (ITT analysis +9.8 %) compared with the improvement after treatment with GS (ITT analysis -11.7 %, p=0.02).
Of the 6 studies of duration greater than 3 months, of one target joint, using relevant regimens, only Pavelka et al (2002) and Reginster et al (2002) provide evidence of superiority of glucosamine relative to placebo. These were both 3 year placebo-controlled trials with appropriate inclusion criteria and relevant endpoints. Results are significant for the WOMAC scale (Reginster et al) and Lequesne scale (Pavelka et al), providing some evidence of efficacy.

**Glucosamine sulphate versus glucosamine hydrochloride**

The majority of the data on clinical efficacy is from studies using GS formulations. Results from 3 studies (see Table 1) provide supportive evidence of the efficacy of GH.

According to the Opinion for Glucomed and associated names (EMEA/405628/2006), the sulphate and hydrochloride forms can be considered interchangeable. Glucosamine is considered highly soluble. Therefore evidence of efficacy of GS formulations can be extrapolated to GH formulations without the need for a comparative bioavailability study.

**Analysis performed across trials (pooled analyses and meta-analysis)**

Twelve meta-analyses from the literature have been summarised. Generally the authors conclude that glucosamine does demonstrate efficacy in osteoarthritis, although several authors recommend further research.

**Assessor’s overall conclusions on clinical efficacy**

There is adequate support from the bibliographic data submitted to support an indication for the relief of symptoms in mild to moderate osteoarthritis of the knee.
Safety
Bibliographic data to support the safety of the proposed product was provided. Sources include meta-analyses and individual clinical efficacy and safety studies. The data is summarised and discussed in the following sections.

Patient exposure
The overall extent of exposure in the individual clinical efficacy studies is 3014 patients, with durations of exposure between 3 weeks and 3 years. Of those patients, 207 were treated with glucosamine for at least 2 years (the combined population of the Pavelka et al. and Reginster et al. studies).

Adverse events
The most common adverse events (AEs) reported in clinical studies were gastrointestinal, generally mild in nature. Other commonly reported AEs include headache and tiredness.

In placebo-controlled trials, the incidence of AEs ranged from 10-93 % and was similar to placebo. In the 4 non-steroid anti-inflammatory drug (NSAID) comparator trials, AEs were consistently higher among those taking NSAIDs.

Serious adverse events and deaths
Deaths
In one study (Pavelka et al. 2002), 1 male patient with a 6 year history of ischemic heart disease with previous myocardial infarctions (MIs), cardiac failure and recent coronary bypass died of a fatal MI before completing 3 months of treatment with the study medication. There was no stated relationship with the treatment.

Serious adverse events
Of the clinical efficacy trials from which safety data has been gathered, events are generally stated as being mild to moderate. Reginster et al. (2001) found that, among the AEs leading to withdrawal, few single episodes were termed serious and all were judged as unrelated to treatment; such episodes were attributable to pre-existing or concomitant conditions in an elderly patient population. In the GAIT study (Clegg et al. 2006), 77 serious adverse events (SAEs) were reported in 61 patients (out of 1583). Three SAEs were judged by the investigator to be related to study treatment, although only two of these were in patients receiving GS; one receiving the combination treatment (GS + CS) had congestive heart failure and one receiving GS alone experienced chest pain.

It is addressed in the SmPC that patients with a known risk factor for cardiovascular disease should have their blood lipid levels monitored.

Laboratory findings
Clinical laboratory data were gathered in some of the clinical efficacy and clinical safety studies. Non-clinical data have indicated that glucosamine might affect glucose homeostasis. Biochemical analysis following the administration of glucosamine in a placebo-controlled trial (Albert et al. 2007) are summarised in Table 2 below. Fasting blood glucose, fructosamine, and cholesterol were stable; furthermore, glucosamine had no effect on high-density lipoprotein (HDL) or apolipoprotein AI levels.
Table 2: The mean ± SD of serum concentrations of glucose, fructosamine, lipid and lipoprotein prior to (pre) and following two weeks of (post) treatment with 1500 mg/d glucosamine or placebo (Albert et al. 2007)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
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<tr>
<td>Glucose, mmol/L</td>
<td>9.5 (5.4)</td>
<td>10.3 (4.9)</td>
<td>9.5 (4.2)</td>
<td>10.5 (6.2)</td>
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<td>Cholesterol, mmol/L</td>
<td>4.16 (0.63)</td>
<td>4.14 (0.77)</td>
<td>4.20 (0.76)</td>
<td>4.19 (0.84)</td>
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<td>HDLc, mmol/L</td>
<td>1.02 (0.15)</td>
<td>1.05 (0.16)</td>
<td>1.04 (0.21)</td>
<td>1.06 (0.16)</td>
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<td>LDLc, mmol/L</td>
<td>2.19 (0.50)</td>
<td>2.26 (0.58)</td>
<td>2.20 (0.65)</td>
<td>2.12 (0.63)</td>
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<td>Triglycerides, mmol/L</td>
<td>2.81 (1.40)</td>
<td>2.64 (1.97)</td>
<td>2.86 (1.51)</td>
<td>3.02 (2.01)</td>
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<td>Fructosamine, µmol/L</td>
<td>309 (104)</td>
<td>330 (139)</td>
<td>298 (74)</td>
<td>327 (97)</td>
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<td>Apoprotein A1, mg/dL</td>
<td>147 (15)</td>
<td>140 (16)</td>
<td>146 (25)</td>
<td>142 (17)</td>
</tr>
<tr>
<td>Apoprotein B, mg/dL</td>
<td>91 (22)</td>
<td>89 (17)</td>
<td>91 (16)</td>
<td>95 (27)</td>
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Several further studies of glucosamine administration have been conducted in healthy volunteers and in diabetic patients, to determine whether glucosamine has a clinically relevant effect upon glucose metabolism in humans, including Scroggie et al. (2003), and as reviewed by Stumpf et al. (2006). The reported clinical laboratory data showed no significant differences in mean blood or plasma glucose concentrations, fasting serum concentrations or HbA1c levels. D’Ambrosio et al. (1981) recorded blood parameters before and after treatment, in OA patients randomised to receive GS or placebo, and found no significant differences. Similarly, in the randomised, placebo-controlled clinical efficacy study by Drovanti et al. (1980), laboratory tests were administered at baseline and at the end of the trial, without any significant differences in values between the GS and placebo groups. Nevertheless, the SmPC states that in patients with impaired glucose tolerance, monitoring of the blood glucose levels and where relevant, insulin requirements are recommended before start of treatment and periodically during treatment.

Safety in special populations
There is no clinical safety data on administration of glucosamine in children, impaired renal function, impaired liver function or pregnant and lactating women. These limitations in the data in these populations have been adequately addressed with various warnings in the SmPC. The proposed warnings are considered acceptable particularly given the proposed indication for relief of symptoms in mild to moderate osteoarthritis of the knee.

Immunological events
The administration of Yointy 625 mg hard capsules to patients who are allergic to shellfish is contraindicated in the SmPC, as the active substance is obtained from shellfish.

Safety related to drug-drug interactions and other interactions
An interaction between glucosamine and warfarin has been identified from The World Health Organisation (WHO) and The Food and Drug Administration (FDA) Medwatch databases (Knudsen et al. 2008); associating concomitant use of glucosamine or glucosamine-chondroitin sulphate and warfarin with altered coagulation manifested by increased International Normalised Ratio (INR), or increased bleeding or bruising. The survey found that in some cases, a decrease in the supplement dosage was followed by a return of the INR to the previous therapeutic range. Similarly, a decrease in warfarin dosage
was also followed by a decrease in international normalised ratio (INR) in one patient who received long-term warfarin therapy. The authors of this database review paper concluded that patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy. The risk of an interaction between warfarin and glucosamine has been adequately covered in the SmPC.

**Post marketing experience**
Tallia *et al* (2002) reported a probable case of asthma exacerbated by the use of a glucosamine-chondroitin sulphate supplement in a patient with underlying intermittent asthma, who may have had a sea squirt allergy. It is stated in the SmPC that asthmatic patients starting on glucosamine should be aware of the potential worsening of symptoms.

**Assessor’s overall conclusions on clinical safety**
Adequate data from the literature regarding the safety of glucosamine have been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are clinically satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA Form**
The MAA form is clinically satisfactory.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Yointy 625 mg hard capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. A satisfactory literature review of published literature was submitted.

EFFICACY
No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required as this was a ‘well established use’ application. A satisfactory literature review of published literature was submitted. No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with glucosamine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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