

GLUCOSAMINE

0.0 OVERVIEW

- A. **GLUCOSAMINE**
- B. **CLASS** : CHONDROPROTECTANT
- C. **DOSAGE** :
 - 1. **IMPORTANT NOTE** : The dosing of dietary supplements is highly dependent on a variety of factors such as quality of raw materials, manufacturing process, and packaging. Since no official standards have been established to date to regulate the production of dietary supplements in the United States, dosage ranges must be employed as guidelines only.
 - 2. **ADULT** :
 - a. **OSTEOARTHRITIS, tablet, oral** : 1500 milligrams in single or 3 divided doses daily.
 - 3. **PEDIATRIC** : Dosing not available.
- D. **ADMINISTRATION** : Intra-articular, intramuscular, intravenous, oral
- E. **HOW SUPPLIED** : Tablet
- F. **USES** :
 - 1. **SCIENTIFIC EVIDENCE** : Glucosamine is effective for osteoarthritis and may be effective for cutaneous aging, knee pain, and temporomandibular joint disorder.
 - 2. **COMPLEMENTARY AND ALTERNATIVE MEDICINE INDICATIONS** : Glucosamine sulfate is used to treat osteoarthritis symptoms although limitations of research must be acknowledged.
- G. **CONTRAINDICATIONS** : Hypersensitivity to glucosamine or any of its components. Use with caution for patients with an allergy to shellfish and shellfish products. Asthma patients may be at risk for an asthma exacerbation when taking the combination of glucosamine and chondroitin. Diabetics should use cautiously as glucosamine may effect insulin sensitivity or glucose tolerance.
- H. **ADVERSE EFFECTS** : Most commonly reported adverse effects include gastrointestinal disturbance, including nausea, dyspepsia, heartburn, vomiting, constipation, diarrhea, anorexia, and epigastric pain. Edema, tachycardia, drowsiness, insomnia, headache, erythema, and pruritus have been reported in less than 1% of patients. The effect on insulin sensitivity and glucose tolerance is unclear and caution is advised for diabetics. Asthma exacerbation was experienced in a previously well-controlled asthmatic taking a glucosamine-chondroitin sulfate supplement.
- I. **DRUG/FOOD INTERACTIONS** : **ANTIDIABETIC AGENTS**: reduced antidiabetic agent effectiveness (theoretical); **DOXORUBICIN**: reduced doxorubicin effectiveness (in vitro data); **ETOPOSIDE**: reduced etoposide effectiveness (in vitro data); **TENIPOSIDE**: reduced teniposide effectiveness (in vitro data)
- J. **PREGNANCY/LACTATION** : Scientific evidence for the safe use of glucosamine during pregnancy and lactation is not available.
- K. **NOTE** : The safety profile of herbal medications and dietary supplements is not well known. Due to the unregulated nature of the supplement industry in the United States, it

is advised to become familiar with manufacturers and their products before recommending them for safe and effective use. Adulteration has been a recurring problem.

1.0 DOSING INFORMATION

1.1 DOSAGE FORMS

- **A. SYNONYMS**

Chitosamine
Glucosamine hydrochloride
Glucosamine sulfate
NSC-758

- **B. TRADE NAMES**

- 1. Trade names for glucosamine sulfate in other countries include Dona(R) and Viartril(R).

1.3 ADULT DOSAGE

- **1.3.1 NORMAL DOSE**

- **A. IMPORTANT NOTE**

- 1. The dosing of dietary supplements is highly dependent on a variety of factors such as quality of raw materials, manufacturing process, and packaging. Since no official standards have been established to date to regulate the production of dietary supplements in the United States, dosage ranges must be employed as guidelines only.

- **B. ORAL**

- 1. **OSTEOARTHRITIS, tablet** : 1500 milligrams daily in single or three divided doses for a minimum of 4 weeks or up to 3 years has been effective (Pavelka et al, 2002; Reginster et al, 2001; Noack et al, 1994).
 - a. Several well-controlled trials demonstrated reduction in pain scores and radiographic improvement in patients with KNEE OSTEOARTHRITIS taking glucosamine sulfate 1500 milligrams daily, single dose or in 3 divided doses, for a minimum of 4 weeks or up to 3 years (Pavelka et al, 2002; Reginster et al, 2000; Noack et al, 1994).
 - b. Glucosamine sulfate 1500 milligrams every day for 6 months improved symptoms of CERVICAL and/or LUMBAR SPINE OSTEOARTHRITIS in a multicenter, randomized, double-blind, placebo-controlled trial (Giacovelli & Rovati, 1993).
- 2. **PAIN, KNEE** : Standard dosing regimens are not available.
 - a. A double-blind, placebo-controlled trial (n=46) demonstrated that glucosamine hydrochloride 2000 milligrams once daily in the morning for 3 months improved chronic knee pain and function (Braham et al, 2003).

- **C. INTRAMUSCULAR**

- 1. **OSTEOARTHRITIS** : Standard dosing regimens are not available.
 - a. Glucosamine sulfate 400 milligrams once daily (Reichelt et al, 1994; D'Ambrosio et al, 1981; Crolle & D'Este, 1980). A regimen

of 400 milligrams twice weekly for 6 weeks has also been given (Reichelt et al, 1994).

- **D. INTRAMUSCULAR**
 - 1. **OSTEOARTHRITIS** : Standard dosing regimens are not available.
 - a. For patients with osteoarthritis, glucosamine sulfate 400 milligrams once daily for one week has been given (D'Ambrosio et al, 1981).
- **E. TOPICAL**
 - 1. **OSTEOARTHRITIS** : Standard dosing regimens are not available.
 - a. **OSTEOARTHRITIS, cream** : A water soluble cream containing 30 milligrams/gram (mg/gram) glucosamine sulfate, 50 mg/grams chondroitin sulfate, and 140 mg/grams shark cartilage was administered to patients with osteoarthritis of the knee for 8 weeks. Patients administered the cream a mean of 2.4 times/day (Cohen et al, 2003).

2.0 PHARMACOKINETICS

2.1 ONSET AND DURATION

- **2.1.1 ONSET**

- **A. INITIAL RESPONSE :**

- 1. Osteoarthritis, oral: 2 to 3 weeks (Reichelt et al, 1994; D'Ambrosio et al, 1981; Crolle & D'Este, 1980; Drovanti et al, 1980; Pujalte et al, 1980).
 - 2. Osteoarthritis, intramuscular: 1 week (Reichelt et al, 1994; D'Ambrosio et al, 1981; Crolle & D'Este, 1980; Drovanti et al, 1980; Pujalte et al, 1980).
 - 3. Osteoarthritis, intravenous: 1 week (Reichelt et al, 1994; D'Ambrosio et al, 1981; Crolle & D'Este, 1980; Drovanti et al, 1980; Pujalte et al, 1980).
 - 4. Osteoarthritis, topical: 1 day (Cohen et al, 2003).
 - a. In addition to glucosamine sulfate, chondroitin sulfate, and shark cartilage, the topical preparation contained both peppermint oil and camphor; these agents may have been responsible for the rapid onset of effect (Cohen et al, 2003).

- **2.1.2 DURATION**

- **A. MULTIPLE DOSE :**

- 1. Osteoarthritis, oral: 4 weeks (McCarty, 1994; Reichelt et al, 1994).

2.2 DRUG CONCENTRATION LEVELS

- **2.2.2 TOXIC**

- A. The LD50 for glucosamine hydrochloride is 15 grams/kilogram (grams/kg) oral, 1100 milligrams/kilogram (mg/kg) intravenous, and 6200 mg/kg subcutaneous in mice (RTECS, 2001).
 - B. 5000 milligrams/kilogram (mg/kg) oral, 3000 mg/kg intramuscular, and 1500 mg/kg intravenous of glucosamine sulfate resulted in no mortality in mice or rats (Kelly, 1998).

2.3 ADME

- **2.3.1 ABSORPTION**

- **A. BIOAVAILABILITY (F) :**

- 1. Intramuscular: 96% (Reichelt et al, 1994; Setnikar et al, 1993).
 - 2. Oral: 26% (Setnikar et al, 1993).
 - a. After oral administration, bioavailability is low due to first-pass hepatic metabolism (Setnikar et al, 1993).
- **2.3.2 DISTRIBUTION**
 - **2.3.2.1 DISTRIBUTION SITES**
 - **A. TOTAL PROTEIN BINDING :**
 - 1. Glucosamine is not protein-bound but rather incorporates into plasma proteins (primarily globulins) (Setnikar et al, 1993).
 - 2. Unbound glucosamine did not bind to plasma proteins of humans, dogs, or rats (Barclay et al, 1998).
 - **2.3.2.2 DISTRIBUTION KINETICS**
 - **A. VOLUME OF DISTRIBUTION (Vd) :** 2.5 Liters (Setnikar et al, 1993).
- **2.3.3 METABOLISM**
 - **2.3.3.1 METABOLISM SITES AND KINETICS**
 - **A. Liver:** extensive (Reichelt et al, 1994; Setnikar et al, 1993).
 - 1. Glucosamine sulfate is rapidly desulfated following oral or parenteral administration. It is metabolized (predominantly in the liver) to smaller molecules and ultimately to carbon dioxide, water, and urea (Reichelt et al, 1994; Setnikar et al, 1993).
- **2.3.4 EXCRETION**
 - **2.3.4.1 BREAST MILK**
 - **A. BREASTFEEDING :** Unknown
 - 1. Scientific evidence for the safe use of glucosamine sulfate during lactation is not available.
 - **2.3.4.2 KIDNEY**
 - **A. RENAL EXCRETION :** 10% (Setnikar et al, 1993).
 - 1. Urinary recovery (radioactivity) accounts for 28% and 37% of radiolabeled intravenous and intramuscular doses, respectively (Setnikar et al, 1993).
 - **2.3.4.3 OTHER**
 - **A. OTHER EXCRETION :**
 - 1. Feces, 11% (Setnikar et al, 1993).
 - a. Approximately 11% of an orally administered dose of radiolabeled glucosamine sulfate was excreted in the feces; most of this appears to be unabsorbed drug. Less than 1% of radioactivity after radiolabeled intravenous or intramuscular doses appear in the feces (Setnikar et al, 1993).
 - 2. Lung, moderate (Setnikar et al, 1993).
 - a. Part of a dose of glucosamine sulfate is eliminated as carbon dioxide via expired air (Setnikar et al, 1993).
- **2.3.5 HALF LIFE**
 - **2.3.5.1 PARENT COMPOUND**

- **A. ELIMINATION HALF-LIFE** : 70 hours (Setnikar et al, 1993).
 - 1. Radiolabeled glucosamine, which was incorporated into plasma proteins, declined slowly with an elimination half-life of 70 hours (Setnikar et al, 1993). In this study, the elimination half-life of glucosamine incorporated into plasma proteins was 68 hours after oral administration and 57 hours after intramuscular administration.

3.0 CAUTIONS

3.1 CONTRAINDICATIONS

- A. Hypersensitivity to glucosamine or any of its components

3.2 PRECAUTIONS

- A. The effect of glucosamine on insulin sensitivity and glucose tolerance is unclear; caution is advised for diabetic patients.
- B. Patients with allergy to shellfish and shellfish products (Prod Info Osteo Bi-Flex, 2003)
- C. Patients with asthma may be at risk for an asthma exacerbation when taking glucosamine-chondroitin sulfate supplement (Tallia & Cardone, 2002)

3.3 ADVERSE REACTIONS

• 3.3.2 CARDIOVASCULAR

• A. CARDIOVASCULAR EFFECTS

- 1. PERIPHERAL EDEMA and TACHYCARDIA were reported in a few patients in larger clinical trials investigating oral or intramuscular glucosamine sulfate in osteoarthritis patients. A causal relationship was not established (Reichelt et al, 1994; Tapadinhas et al, 1982).

• 3.3.3 CENTRAL NERVOUS SYSTEM

• A. CENTRAL NERVOUS SYSTEM EFFECTS

- 1. DROWSINESS, HEADACHE, and INSOMNIA have been rarely observed during therapy with oral glucosamine sulfate (less than 1% of patients) (Barclay et al, 1998; Qiu et al, 1998; Tapadinhas et al, 1982).

• 3.3.4 ENDOCRINE/METABOLIC

• A. ENDOCRINE EFFECTS

• 1. INSULIN SENSITIVITY AND GLUCOSE TOLERANCE

• a. SUMMARY :

- (1) Clinical studies are inconclusive regarding the effect of glucosamine on glucose and insulin sensitivity. The Arthritis Foundation has recommended that diabetics monitor their blood glucose more frequently when taking glucosamine (Anon, 2002). Controlled clinical trials evaluating the efficacy of glucosamine sulfate in knee osteoarthritis have not demonstrated a significant change in blood glucose levels. In a trial of 212 patients, blood glucose levels were slightly decreased, even after 3 years (Reginster et al, 2001). In a second three-year study of 202 patients, diabetic patients were excluded, though 3 patients taking placebo and 1 patient taking glucosamine were

diagnosed with diabetes (Pavelka et al, 2002). The number of patients with diabetes or glucose intolerance was not reported in many studies (Reginster et al, 2001; Towheed & Anastassiades, 1999; Rindone et al, 2000; Houpt et al, 1999; Leffler et al, 1999). In 15 nondiabetic patients, 12 weeks of glucosamine treatment did not affect fasting glucose but did increase fasting insulin versus placebo ($p=0.01$) (Almada et al, 2000). In 5 healthy subjects, intravenous glucosamine sulfate reduced glucose tolerance and insulin sensitivity under hyperglycemic conditions (Monauni et al, 2000) whereas glucosamine infusion did not affect insulin-induced glucose uptake in 18 healthy subjects (Pouwels et al, 2001). Several rat studies have shown glucosamine infusions to induce insulin resistance (Holmang et al, 1999; Shankar et al, 1998; Rossetti et al, 1995; Balkan & Dunning, 1994) while one rat study demonstrated no effect (Echard et al, 2001).

- **b. LITERATURE :**

- (1) Decreased glucose tolerance, glucose clearance, insulin sensitivity, and glucose effectiveness were observed under hyperglycemic conditions in 5 healthy subjects receiving intravenous glucosamine sulfate (5 micromoles/minute/kilogram (mcmol/min/kg) for 6 hours) (p less than 0.01 to 0.05). During euglycemia, glucosamine did not affect any of these parameters. A lower dose of glucosamine (1.6 mcmol/min/kg) did not affect any of these parameters in 10 healthy volunteers. The authors concluded that glucosamine may be a competitive inhibitor of glucokinase in pancreatic beta cells (Monauni et al, 2000). The applicability of this intravenous dose to that taken orally in a therapeutic dose is unclear.

- **3.3.5 GASTROINTESTINAL**

- **A. GASTROINTESTINAL EFFECTS**

- 1. Gastrointestinal symptoms of NAUSEA, DYSPEPSIA, VOMITING, abdominal or EPIGASTRIC PAIN, CONSTIPATION, DIARRHEA, HEARTBURN, and ANOREXIA have been rarely described during oral therapy of osteoarthritis with glucosamine sulfate (Barclay et al, 1998; daCamara & Dowless, 1998; Qiu et al, 1998; Mueller-Fassbender et al, 1994; Tapadinhas et al, 1982; Drovanti et al, 1980). In a large open trial ($n=1208$), the most common adverse effects with oral glucosamine sulfate (1.5 grams daily) were epigastric pain/tenderness (3.5%), heartburn (2.7%), diarrhea (2.5%), and nausea (1%) (Tapadinhas et al, 1982).
- 2. The only gastrointestinal effects observed with intramuscular glucosamine sulfate were nausea and vomiting and these rarely occurred (Reichelt et al, 1994).

- **3.3.9 RESPIRATORY**

- **A. ASTHMA**
 - 1. A fifty-two-year-old woman with well-controlled asthma experienced an exacerbation of symptoms with the initiation of glucosamine-chondroitin sulfate for osteoarthritis. She complained of **SHORTNESS OF BREATH** and **WHEEZING**. Her condition did not improve despite treatment with oral steroids and increased albuterol inhaler doses. Within 24 hours after discontinuation of glucosamine-chondroitin, the patient's asthma symptoms abated and returned to a well-controlled state (Tallia et al, 2002). A Medline literature search found a possible relationship between atopic conditions, including asthma, and glucosamine-chondroitin supplementation (Tallia et al, 2002).
- **3.3.10 SKIN**
 - **A. DERMATOLOGIC EFFECTS**
 - 1. Local injection-site pain has occurred rarely with intramuscular glucosamine sulfate (Reichelt et al, 1994). Skin reactions such as **ERYTHEMA** and **PRURITUS** have been rare complications of oral or intramuscular glucosamine sulfate (Barclay et al, 1998; Reichelt et al, 1994; Tapadinhas et al, 1982).
 - 2. Erythema and pruritus have been rare complications of oral or intramuscular glucosamine sulfate (Reichelt et al, 1994; Tapadinhas et al, 1982).

3.4 TERATOGENICITY/EFFECTS IN PREGNANCY

- **3.4.A TERATOGENICITY**
 - 1. No human or animal teratogenicity data available.
- **3.4.B EFFECTS IN PREGNANCY**
 - 1. Scientific evidence for the safe use of glucosamine during pregnancy is not available.

3.5 DRUG INTERACTIONS

- **3.5.1 DRUG-DRUG COMBINATIONS**
 - **A. ANTIDIABETIC AGENTS**
 - 1. **SUMMARY** : Glucosamine did not affect hemoglobin A1c in a randomized, double-blind, placebo-controlled trial of 34 patients with well-controlled type 2 diabetes mellitus (Scroggie et al, 2003). The results of this trial may not apply to patients with uncontrolled diabetes. The Arthritis Foundation has recommended that patients with diabetes monitor their blood glucose more frequently when taking glucosamine (Anon, 2002). Clinical studies are inconclusive regarding the effect of glucosamine on glucose and insulin sensitivity (Pavelka et al, 2002; Pouwels et al, 2001; Reginster et al, 2001; Almada et al, 2000; Monauni et al, 2000).
 - 2. **ADVERSE EFFECT** : reduced antidiabetic agent effectiveness
 - 3. **CLINICAL MANAGEMENT** : Glucosamine is likely safe for patients with diabetes that is well-controlled with diet only or with one or two oral antidiabetic agents (HbA1c less than 6.5%). In patients with higher HbA1c concentrations or for those requiring insulin, closely monitor blood glucose concentrations.

- 4. **SEVERITY** : minor
- 5. **ONSET** : rapid
- 6. **DOCUMENTATION** : fair
- 7. **PROBABLE MECHANISM** : impaired insulin secretion through competitive inhibition of glucokinase in pancreatic beta cells and/or alteration of peripheral glucose uptake
- 8. **LITERATURE REPORTS** :
 - a. Glucosamine did not significantly affect hemoglobin A1c (HbA1c) in a randomized, double-blind, placebo-controlled trial of 34 patients with well- controlled type 2 diabetes mellitus. Patients received glucosamine (Cosamin DS) 1500 milligrams (mg) (n=22) or placebo (n=12) daily for 90 days. The Cosamin DS also contained chondroitin sulfate 400 mg, manganese 5 mg, and ascorbic acid 66 mg. HbA1c increased from a mean baseline of 6.45% to 6.5% in the glucosamine group, and decreased from a mean baseline of 6.25% to 6.09% in the placebo group (not significant). The study had 80% power to detect a difference of greater than 0.3% between groups, and 80% power to detect a difference of 0.15% from before to after treatment in the glucosamine group (Scroggie et al, 2003).
 - b. In a trial of 212 non-diabetic patients taking glucosamine for knee osteoarthritis, blood glucose levels were slightly decreased after 3 years versus placebo (Reginster et al, 2001). In a second three-year study of 202 non-diabetic patients, 3 patients taking placebo and one patient taking glucosamine were diagnosed with diabetes (Pavelka et al, 2002). In 15 nondiabetic patients, 12 weeks of glucosamine treatment did not affect fasting glucose, but did increase fasting insulin versus placebo (p = 0.01) (Almada et al, 2000). In 5 healthy subjects, intravenous glucosamine sulfate reduced glucose tolerance and insulin sensitivity under hyperglycemic conditions (Monauni et al, 2000), whereas glucosamine infusion did not affect insulin-induced glucose uptake in 18 healthy subjects (Pouwels et al, 2001).
- **B. DOXORUBICIN**
 - 1. **SUMMARY** : Glucosamine induced resistance to the topoisomerase II inhibitors doxorubicin and etoposide in human colon and ovarian cancer cells in vitro (Yun et al, 1995), and induced resistance to doxorubicin and teniposide in vitro in EMT6 cancer cells (Russell et al, 1993). The clinical effect of glucosamine taken orally is unknown; it is possible that glucosamine may confer resistance to doxorubicin in humans. Avoid glucosamine in patients being treated with doxorubicin.
 - 2. **ADVERSE EFFECT** : reduced doxorubicin effectiveness
 - 3. **CLINICAL MANAGEMENT** : Avoid concomitant use of glucosamine with doxorubicin.
 - 4. **SEVERITY** : moderate
 - 5. **ONSET** : rapid

- 6. **DOCUMENTATION** : poor
- 7. **PROBABLE MECHANISM** : induction of glucose-regulated stress proteins resulting in diminished expression of topoisomerase II
- **C. ETOPOSIDE**
 - 1. **SUMMARY** : Glucosamine induced resistance to the topoisomerase II inhibitors etoposide and doxorubicin in vitro in human colon and ovarian cancer cells (Yun et al, 1995), and induced resistance to doxorubicin and teniposide in vitro in EMT6 cancer cells (Russell et al, 1993). The clinical effect of glucosamine taken orally is unknown; it is possible that glucosamine may confer resistance to etoposide in humans. Avoid glucosamine in patients being treated with etoposide.
 - 2. **ADVERSE EFFECT** : reduced etoposide effectiveness
 - 3. **CLINICAL MANAGEMENT** : Avoid concurrent use of glucosamine and etoposide.
 - 4. **SEVERITY** : moderate
 - 5. **ONSET** : rapid
 - 6. **DOCUMENTATION** : poor
 - 7. **PROBABLE MECHANISM** : induction of glucose-regulated stress proteins resulting in decreased expression of topoisomerase II
- **D. TENIPOSIDE**
 - 1. **SUMMARY** : Glucosamine induced resistance to the topoisomerase II inhibitor teniposide in vitro in EMT6 cancer cells (Russell et al, 1993), and induced resistance to the topoisomerase II inhibitors etoposide and doxorubicin in vitro in human colon and ovarian cancer cells (Yun et al, 1995). The clinical effect of glucosamine taken orally is unknown; it is possible that glucosamine may confer resistance to teniposide in humans. Avoid glucosamine in patients being treated with teniposide.
 - 2. **ADVERSE EFFECT** : reduced teniposide effectiveness
 - 3. **CLINICAL MANAGEMENT** : Avoid concurrent use of glucosamine and teniposide.
 - 4. **SEVERITY** : moderate
 - 5. **ONSET** : rapid
 - 6. **DOCUMENTATION** : poor
 - 7. **PROBABLE MECHANISM** : induction of glucose-regulated stress proteins resulting in diminished expression of topoisomerase II

4.0 CLINICAL APPLICATIONS

4.1 MONITORING PARAMETERS

• 4.1.1 THERAPEUTIC

• A. PHYSICAL EXAMINATION

- 1. Periodic assessment of pain at rest or during movement, ability to move freely, and walking distance in osteoarthritis patients.
- 2. Radiographic evaluations (eg, joint space narrowing).

• 4.1.2 TOXIC

• A. LABORATORY PARAMETERS

- 1. Routine blood chemistry

4.3 PLACE IN THERAPY

- **A. SUMMARY OF SCIENTIFIC EVIDENCE :**
 - 1. **CUTANEOUS AGING** : Oral glucosamine with a mixture of antioxidants decreased the number of wrinkles in a small trial.
 - 2. **OSTEOARTHRITIS** : Multiple short-term studies have demonstrated reductions in pain scores and radiographic improvement for patients with osteoarthritis supplemented with glucosamine.
 - 3. **PAIN, KNEE** : A small trial of patients with unspecified knee pain demonstrated reduction in pain but minimal improvement in clinical and functional tests.
 - 4. **TEMPOROMANDIBULAR JOINT DISORDER** : A combination glucosamine and chondroitin supplement decreased the sounds associated with temporomandibular joint disorder (TMJ) and a reduction of over-the-counter medication required for pain relief.
- **B. COMMON USES IN COMPLEMENTARY AND ALTERNATIVE MEDICINE :** Glucosamine sulfate is used for the symptoms of osteoarthritis although some limitations of the available research must be acknowledged. The knee is the most common site of pathological involvement studied and treatment length has usually been less than 4 months. Whether long-term use of glucosamine can reverse the course of osteoarthritis is a theory that has yet to be investigated. Speculative use of glucosamine in arthritis prevention and articular injury repair also remain to be studied.
- **C. REGULATORY/SAFETY INFORMATION :** Glucosamine is currently classified by the International League Against Rheumatism as a Symptomatic Slow- Acting Drug in Osteoarthritis (SYSADOA); this group is characterized by slow-onset improvement in osteoarthritis and persistent benefits after discontinuation (Higgins, 1993). Glucosamine is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

4.4 MECHANISM OF ACTION/PHARMACOLOGY

- **A. MECHANISM OF ACTION**
 - 1. **SUMMARY** : Glucosamine (2-amino-2-deoxy beta-D-glucopyranose) is an endogenous aminomonosaccharide synthesized from glucose and utilized for biosynthesis of glycoproteins and glycosaminoglycans (Reichelt et al, 1994; Reuser & Wisselaar, 1994; Setnikar et al, 1993). Due to early studies suggesting altered glucosamine metabolism contributing to the development of osteoarthritis, glucosamine has been investigated clinically in this disorder as the sulfate salt (D'Ambrosio et al, 1981; Pujalte et al, 1980).
 - 2. **ANTI-ARTHRITIC** :
 - a. Glucosamine (2-amino-2-deoxy beta-D-glucopyranose) is an endogenous aminomonosaccharide synthesized from glucose and utilized for biosynthesis of glycoproteins and glycosaminoglycans (Runkel & Cupp, 1999; Reichelt et al, 1994; Reuser & Wisselaar, 1994; Setnikar et al, 1993). The sulfate salt of glucosamine forms half of the disaccharide subunit of keratan sulfate, which is decreased in osteoarthritis, and of hyaluronic acid, which is found in both articular cartilage and synovial fluid (Leffler et al, 1999). Due to early studies suggesting altered glucosamine metabolism contributing to the development of osteoarthritis

(D'Ambrosio et al, 1981; Pujalte et al, 1980), glucosamine has been investigated clinically in this disorder as the sulfate salt.

- b. Preclinical studies with glucosamine have suggested tropism of this compound for cartilage and bone and that it may serve as a preferred substrate for (and stimulant of) proteoglycan biosynthesis; the proteoglycans are essential components of articular cartilage (Setnikar et al, 1993; D'Ambrosio et al, 1981; Vidal y Plana et al, 1978). Exogenous administration of glucosamine in animals has been reported to retard cartilage degradation and rebuild experimentally damaged cartilage tissue (D'Ambrosio et al, 1981; Pujalte et al, 1980; Crolle & D'Este, 1980). Glucosamine enhances cartilage proteoglycan synthesis, thereby inhibiting deterioration of cartilage brought about by osteoarthritis and helping to maintain equilibrium between cartilage catabolic and anabolic processes (Vidal y Plana & Karzel, 1980). Protection against metabolic impairment of cartilage induced by nonsteroidal anti-inflammatory drugs and corticosteroids has been described (Reichelt et al, 1994; Vidal y Plana et al, 1978). An anti-inflammatory action of glucosamine has also been proposed, unrelated to cyclooxygenase inhibition (Reichelt et al, 1994).
- **3. ATHEROGENESIS :**
 - a. By analogy with heparin, glucosamine may be useful in the prevention of atherogenesis and thrombus formation by a stimulatory effect on production of heparin sulfate polyglycans which inhibits migration, multiplication, and cell-type transition of vascular smooth endothelial cells. This potential effect is hypothetical and has not yet been tested, even in cell cultures (McCarty, 1997).
- **4. GLUCOSE METABOLISM EFFECT :**
 - a. It has been hypothesized that glucosamine may impair insulin secretion through competitive inhibition of glucokinase in pancreatic beta cells and/or alteration of peripheral glucose uptake (Monauni et al, 2000; Balkan & Dunning, 1994).
- **5. WOUND HEALING EFFECT :**
 - a. It has been hypothesized that oral glucosamine will enhance hyaluronic acid synthesis, thus accelerating healing and minimizing scarring in fresh wounds. Hyaluronic acid (HA), synthesized by fibroblasts, promotes proliferation of epithelial cells. HA is a polysaccharide with disaccharide units consisting of glucuronic acid in a beta 1-3 linkage with N-acetylglucosamine. Glucosamine can be synthesized intracellularly; however, the rate of production of HA is markedly increased by exogenous glucosamine (McCarty, 1996).
- **B. REVIEW ARTICLES**
 - **1. ENGLISH**
 - a. A meta-analysis of 15 clinical trials concerning the use of glucosamine and chondroitin in the treatment of osteoarthritis is available (McAlindon et al, 2000).
 - b. The pharmacology and pharmacokinetics of glucosamine are reviewed with a critical evaluation of its safety and efficacy (Barclay et al, 1998).

- c. Clinical trials evaluating the usefulness of glucosamine sulfate in the treatment of patients with osteoarthritis are reviewed (da Camara & Dowless, 1998).
- d. Recommendations by the Journal of Family Practice are available (Preibe et al, 2003).

4.5 THERAPEUTIC USES

- **A. CUTANEOUS AGING**

- **1. OVERVIEW :**

EFFICACY: Adult, possibly effective

DOCUMENTATION: Adult, fair

- **2. SUMMARY :**

- Treatment with an oral supplement containing antioxidants, minerals, and glucosamine decreased the number of wrinkles as measured by silflo replica

- **3. ADULT :**

- a. A reduction in the number of visible wrinkles and fine lines was noted following 6 weeks of treatment of an oral supplement containing antioxidants, minerals, and glucosamine. Fifty-three women (mean age 46.1 years; range 39 to 56 years) in a single-blind study were given an oral supplement containing N-acetyl D-glucosamine, glucosamine sulfate, L-proline, L-lysine, manganese, copper, zinc, quercetin, and grape seed extract twice daily (doses not specified) for 5 weeks. Twelve women who did not receive the oral supplement served as controls. As measured by silflo replicas, there was a significant reduction (34%) in the number of visible wrinkles between the treated patients and control group (p less than 0.01). A 34% reduction was also measured in the number of fine lines; however, this did not achieve statistical significance (p less than 0.06). There were no significant changes in the hydration level of the stratum corneum in either group as hydration levels can affect the appearance of wrinkles and fine lines (Murad & Tabiban, 2001).

- **B. OSTEOARTHRITIS**

- **1. OVERVIEW :**

EFFICACY: Adult, effective

DOCUMENTATION: Adult, good

- **2. SUMMARY :**

- A meta-analysis demonstrated that glucosamine improved pain, function, and joint mobility, and though data are sparse, improved joint space narrowing in patients with knee or hip osteoarthritis

- Multiple studies up to 3 years duration demonstrated reduction in pain scores and radiographic improvement in patients with knee osteoarthritis
- Glucosamine may have potential as a disease modifying agent
- A minimum duration of 4 weeks of glucosamine was administered in studies with positive outcomes
- Long term trials are needed to fully assess the effectiveness of glucosamine in osteoarthritis
- **3. ADULT :**
 - **a. POSITIVE RESULTS**
 - (1) A topical preparation of glucosamine, chondroitin, and shark cartilage reduced pain associated with osteoarthritis of the knee. Sixty-three patients were randomized to receive a water soluble cream (containing 30 milligrams/gram (mg/gram) glucosamine sulfate, 50 mg/gram chondroitin sulfate, 140 mg/gram shark cartilage, 32 mg/gram camphor, and 9 mg/gram peppermint oil) or placebo for 8 weeks. Both groups reported improvement of the visual analog scale pain scores with the treatment group improving a further 1.2 points ($p=0.03$) at four weeks and 1.8 points ($p=0.002$) at eight weeks compared to the placebo group. Patients were instructed to apply cream generously to painful joints, gently massage until cream disappears, and repeat as necessary (Cohen et al, 2003).
 - (2) A meta-analysis of 15 randomized, placebo-controlled trials evaluating the structural and symptomatic efficacy of oral glucosamine and chondroitin in knee osteoarthritis demonstrated efficacy for glucosamine on joint space narrowing (JSN) and Western Ontario MacMaster University Osteoarthritis Index (WOMAC). Similar efficacies were demonstrated for chondroitin and glucosamine on the Lequesne Index (LI) and visual analogue scale (VAS) for pain and mobility. Joint cartilage degeneration was slowed by the long term daily administration of oral glucosamine at the minimal dose of 1500 milligrams during a minimal period of 3 years (Richy et al, 2003).
 - (3) A meta-analysis of 15 double-blind, randomized, placebo-controlled trials of oral or parenteral glucosamine sulfate, glucosamine hydrochloride, and chondroitin sulfate for knee or hip osteoarthritis concluded that some degree of efficacy was likely, despite quality concerns. Data from 6 glucosamine trials encompassed four published articles plus two abstracts, all involving knee osteoarthritis. One study employed intra-articular

glucosamine while the remainder used oral formulations. All but one trial had ties to a drug manufacturer. Allocation concealment was inadequate and intent-to-treat analyses were absent in five of six glucosamine trials. The quality scores ranged from 12.3% to 51.9%. An asymmetric funnel plot suggested a high likelihood of publication bias. The pooled treatment effect size for glucosamine was 0.44 (95% confidence interval, 0.24 to 0.64) which is considered moderate (McAlindon et al, 2000). An accompanying editorial noted the lack of information provided about sample demographics, long-term efficacy, and potential for toxicity. Definitive conclusions must await completion of high quality, independent studies (Towheed & Anastassiades, 1999).

- (4) Glucosamine sulfate 1500 milligrams orally once daily for 3 years significantly decreased progression of joint space narrowing measured radiographically in a randomized, double-blind, placebo-controlled study of 202 patients with moderate knee osteoarthritis lasting longer than 10 years. Glucosamine reduced joint space narrowing at the end of each year of the study. At year 3, patients receiving placebo had joint space narrowing of -0.19 millimeters (mm) while patients taking glucosamine had a slight increase in joint space (+0.04 mm) ($p=0.001$ between groups). Symptoms, assessed by Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index and the Lequesne index, improved 15% and 20% over baseline with glucosamine (p less than 0.001 and $p=0.002$, respectively) compared with placebo. Fewer patients taking glucosamine than those taking placebo experienced severe joint damage progression, defined as greater than 0.5 mm joint space narrowing (5 versus 14, $p=0.05$). Atlas osteophyte scores worsened in more placebo patients than glucosamine patients (11 of 56 versus 4 of 66, $p=0.03$). The authors suggested that this may support use of glucosamine for early intervention, though such use requires further study (Pavelka et al, 2002).
- (5) Glucosamine sulfate 1500 milligrams orally once daily significantly (p less than 0.05) prevented knee joint structural changes in subjects with osteoarthritis over a three-year period in a randomized, double-blind, placebo-controlled study. The placebo group ($n=106$) had progressive joint space narrowing and a mean loss after 3 years of - 0.31 millimeters (mm) (95% confidence interval (CI) -0.48 to -0.13). The glucosamine group ($n=106$) had no significant joint space loss (- 0.06 mm (95% CI -0.22 to -0.09)). Symptoms, assessed by Western Ontario and McMaster Universities (WOMAC) scores, slightly worsened in the placebo group but improved 20% to 25% in the treatment group. The difference between placebo and glucosamine group symptom scores was significant ($p=0.016$). WOMAC sub-scale scores

measuring pain and physical function were significant for improvement with glucosamine group compared to placebo ($p=0.047$ for pain and $p=0.020$ for physical function) but only minor changes in stiffness were noted between groups. The authors suggested that glucosamine sulfate may be of use as a disease modifying agent for osteoarthritis (Reginster et al, 2001).

- (6) Oral glucosamine sulfate improved symptoms of knee osteoarthritis compared to placebo in a randomized, double-blind, placebo-controlled, multicenter study of 252 patients. Patients had to have knee osteoarthritis for a least 6 months and a radiographic Lequesne index of at least 4. Patients received glucosamine sulfate 500 milligrams orally three times daily for 4 weeks. Response, defined as a decrease of at least 3 points in the Lequesne index, occurred in 55% of patients receiving glucosamine and 38% of patients in the placebo group ($p=0.014$). The average decrease in the Lequesne index with glucosamine was 3.2 points and 2.2 points with placebo. Statistical significance was achieved only in the fourth week of treatment. Adverse effects reported with glucosamine were gastrointestinal disturbance (5 with glucosamine (3 withdrawals), 6 with placebo (5 withdrawals), and headache (2 with glucosamine (2 withdrawals), and 2 with placebo (1 withdrawal) (Noack et al, 1994).
- (7) Oral glucosamine was effective for osteoarthritis of the spine in a multicenter, randomized, double-blind, placebo-controlled trial. Subjects ($n=160$) with symptomatic cervical and/or lumbar spine osteoarthritis of at least 6 months duration received glucosamine sulfate 1500 milligrams daily or placebo for 6 weeks. Outcome measures included visual analogue scales and/or clinical measurements for pain, morning stiffness, tenderness, and mobility. Analysis of variance found significant improvement compared to placebo at both locations for pain at rest and at night, tenderness and lateral flexion, and at the lumbar level for pain on active movement, flexion, rotation, and morning stiffness. Improvement persisted 4 weeks after discontinuation of treatment (Giacovelli & Rovati, 1993).
- (8) Combination therapy with glucosamine, chondroitin, and manganese ascorbate improved knee arthritis symptoms but had equivocal effects on low back arthritis in a 16-week, randomized, double-blind, placebo-controlled, cross-over pilot study involving 34 men from the United States Navy diving and special warfare community. After a 3-week baseline run-in, subjects were randomized to receive either oral Cosamin (consisting of glucosamine hydrochloride 500 milligrams (mg), chondroitin sulfate 400 mg, and manganese ascorbate 76 mg) or placebo three times daily for 8 weeks. After a 5-week washout period, subjects crossed over to the other regimen. Overall, improvement under

treatment was statistically significant by patient assessment of results ($p=0.02$) and the visual analog scale for pain, both recorded in examinations ($p=0.02$) or in patient diaries ($p=0.02$). On medication, 10 patients noted knee improvement, 2 noted knee worsening, and the remainder were unchanged, compared with placebo ($p=0.04$). The mean change in physical examination scores demonstrated significant improvement ($p=0.01$) for treated patients, although changes in discrete subscores of tenderness, effusion, swelling, and warmth did not reach significance. Running times and knee range of motion were unaffected by treatment and trends in acetaminophen use, Lequesne scores, and patient and examiner assessment of severity did not reach significance (Leffler et al, 1999).

- (9) Intramuscular glucosamine was superior to placebo in a placebo- controlled, multicenter study. Patients with mono or bilateral osteoarthritis of the knee were given intramuscular glucosamine sulfate 400 milligrams ($n=79$) or placebo ($n=76$) twice weekly for 6 weeks. The response rate based on the radiographic Lequesne index (pain, walking distance, movement limitations) and investigator evaluations of overall efficacy (subjective scale ranging from "good" to "worse") was 55% with glucosamine and 33% with placebo. Improvements seen with glucosamine persisted during a 2-week follow-up period. This study overcame some of the flaws of previous trials by providing more extensive diagnostic information and better descriptions of study subjects. Other problems, however, emerged, including lack of randomization and missing data, such as symptom severity at baseline. A definition of what constituted response categories ("good" to "worse") was lacking, and it is not clear if the same evaluation methods were used from center to center. The definition of percentage of responders with respect to time was not presented; it is uncertain if this percentage represented any response at all during treatment or those responding after 6 weeks. Clinical improvement on the Lequesne index (main evaluation parameter) was barely significant in favor of glucosamine and only during weeks 5 and 6 of treatment. This may have been related to twice weekly dosing or the slow onset of action. Regardless of this consideration, the clinical significance of the differences observed is questionable and since the severity of symptomatology in each group was not clear, the difference is essentially meaningless. A longer treatment period (eg, 12 weeks) would have enabled more appropriate evaluation of efficacy (Reichelt et al, 1994).
- **b. EQUIVOCAL RESULTS**
 - (1) Glucosamine was no better than placebo as an analgesic for patients with osteoarthritis of the knee in a randomized, double-blind, parallel trial. In a 6-month evaluation, patients with varying

degrees of pain were randomized to receive glucosamine sulfate 500 milligrams 3 times daily (n=38) or placebo (n=37). Patients were assessed using the visual analog scale, Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and the McGill pain questionnaire at baseline, 6, 12 and 24 weeks. There were no differences between the groups in any marker at any time during the trial. The authors suggested that the results of this trial differ from previous glucosamine studies because their patients were more symptomatic and had more structural damage than patients in trials with positive glucosamine results. In addition, this trial had a high placebo response of 33%, perhaps an indication of selection bias to those who have an affinity for complementary therapies (Hughes & Carr, 2002).

- (2) Glucosamine was no better than placebo in reducing pain from osteoarthritis of the knee in a randomized, double-blind, parallel trial. Patients with a history of osteoarthritis of the knee were randomly assigned to orally receive 500 milligrams glucosamine three times daily (n=49) or a placebo (n=49) for two months. Pain was evaluated with a visual analog scale and participants were evaluated at days 0, 30, and 60. No statistical difference was noted between the glucosamine group and the placebo group in mean scores for resting and walking after 30 and 60 days (Rindone et al, 2000).
- (3) No significant improvement was reported for patients who received glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. The trial began with a two-week washout period at which time patients were interviewed and examined and received 500 milligram (mg) acetaminophen caplets to be taken for knee pain as necessary (with a maximum of eight caplets daily). At week zero, patients were randomized to receive glucosamine hydrochloride (500 mg capsules) or placebo three times daily before meals in addition to acetaminophen. The trial lasted eight weeks, followed by a further 2-month open label study. Patients were evaluated based on total scores of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), as well as a daily diary kept by patients each evening and returned at weeks zero, four, and eight. Overall results of the WOMAC questionnaire suggested improvement in the glucosamine treated group (n=45) versus the placebo group (n=53); however, none of the p values were statistically significant. Diary data indicated that the glucosamine group had greater improvement each week while the placebo group had improvement only in the week following their interaction with research staff. Knee examination data for the glucosamine group indicated improvement versus placebo beginning week 4. Adverse effects were about the same in each group (12%) and consisted of mild gastrointestinal symptoms, such

as gas, abdominal bloating, and/or cramps. During the open label phase, all participants (n=83) took glucosamine and 77% continued thereafter (Houpt et al, 1999).

- **C. PAIN, KNEE**

- **1. OVERVIEW :**

EFFICACY: Adult, possibly effective

DOCUMENTATION: Adult, good

- **2. SUMMARY :**

- In various trials, patients reported positive and negative improvement in knee pain when treated with glucosamine

- **3. ADULT :**

- **a. POSITIVE STUDIES**

- (1) Patients reported improvement in unspecified knee pain and function after glucosamine supplementation. In a randomized, placebo-controlled study, patients received glucosamine hydrochloride 2000 milligrams (n=24) or placebo (n=22) once daily in the morning for 3 months. Between the groups, there was no difference in joint line palpation, duck walk, and stair climb results. There were significant improvements in the glucosamine group on the knee pain scale at week 8 of evaluation (p=0.004) and on the knee injury and osteoarthritis outcome score (KOOS) on weeks 8 and 12 (p=0.038). Self-reported improvements in perceived pain began to occur between weeks 4 and 8 and at week 12. Eighty-eight per cent of patients who were receiving glucosamine reported some level of pain relief, compared to 17% in the placebo group. Side effects were reported as mild and short lived, with the gastrointestinal effects and headache occurring most frequently and equally between groups (Braham et al, 2003).
- (2) A topical preparation of glucosamine, chondroitin, and shark cartilage reduced pain associated with osteoarthritis of the knee. Sixty-three patients were randomized to receive a water soluble cream (containing 30 milligrams/gram (mg/gram) glucosamine sulfate, 50 mg/gram chondroitin sulfate, 140 mg/gram shark cartilage, 32 mg/gram camphor, and 9 mg/gram peppermint oil) or placebo for 8 weeks. Both groups reported improvement of the visual analog scale pain scores with the treatment group improving a further 1.2 points (p=0.03) at four weeks and 1.8 points (p=0.002) at eight weeks compared to the placebo group. Patients were instructed to apply cream generously to painful joints, gently massage until cream disappears, and repeat as necessary (Cohen et al, 2003).
- (3) Oral glucosamine was effective for osteoarthritis of the spine in a multicenter, randomized, double-blind, placebo-controlled trial.

Subjects (n=160) with symptomatic cervical and/or lumbar spine osteoarthritis of at least 6 months duration received glucosamine sulfate 1500 milligrams daily or placebo for 6 weeks. Outcome measures included visual analogue scales and/or clinical measurements for pain, morning stiffness, tenderness, and mobility. Analysis of variance found significant improvement compared to placebo at both locations for pain at rest and at night, tenderness and lateral flexion, and at the lumbar level for pain on active movement, flexion, rotation, and morning stiffness. Improvement persisted 4 weeks after discontinuation of treatment (Giacovelli & Rovati, 1993).

- (4) A topical preparation of glucosamine, chondroitin, and shark cartilage reduced pain associated with osteoarthritis of the knee. Sixty-three patients were randomized to receive a water soluble cream (containing 30 milligrams/gram (mg/gram) glucosamine sulfate, 50 mg/gram chondroitin sulfate, 140 mg/gram shark cartilage, 32 mg/gram camphor, and 9 mg/gram peppermint oil) or placebo for 8 weeks. Both groups reported improvement of the visual analog scale pain scores with the treatment group improving a further 1.2 points ($p=0.03$) at four weeks and 1.8 points ($p=0.002$) at eight weeks compared to the placebo group. Patients were instructed to apply cream generously to painful joints, gently massage until cream disappears, and repeat as necessary (Cohen et al, 2003).
- **b. EQUIVOCAL RESULTS**
 - (1) Glucosamine was no better than placebo as an analgesic for patients with osteoarthritis of the knee in a randomized, double-blind, parallel trial. In a 6-month evaluation, patients with varying degrees of pain were randomized to receive glucosamine sulfate 500 milligrams 3 times daily (n=38) or placebo (n=37). Patients were assessed using the visual analog scale, Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and the McGill pain questionnaire at baseline, 6, 12 and 24 weeks. There were no differences between the groups in any marker at any time during the trial. The authors suggested that the results of this trial differ from previous glucosamine studies because their patients were more symptomatic and had more structural damage than patients in trials with positive glucosamine results. In addition, this trial had a high placebo response of 33%, perhaps an indication of selection bias to those who have an affinity for complementary therapies (Hughes & Carr, 2002).
 - (2) Glucosamine was no better than placebo in reducing pain from osteoarthritis of the knee in a randomized, double-blind, parallel trial. Patients with a history of osteoarthritis of the knee were randomly assigned to orally receive 500 milligrams glucosamine three times daily (n=49) or a placebo (n=49) for two months. Pain

was evaluated with a visual analog scale and participants were evaluated at days 0, 30, and 60. No statistical difference was noted between the glucosamine group and the placebo group in mean scores for resting and walking after 30 and 60 days (Rindone et al, 2000).

- (3) No significant improvement was reported for patients who received glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. The trial began with a two-week washout period at which time patients were interviewed and examined and received 500 milligram (mg) acetaminophen caplets to be taken for knee pain as necessary (with a maximum of eight caplets daily). At week zero, patients were randomized to receive glucosamine hydrochloride (500 mg capsules) or placebo three times daily before meals in addition to acetaminophen. The trial lasted eight weeks, followed by a further 2-month open label study. Patients were evaluated based on total scores of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), as well as a daily diary kept by patients each evening and returned at weeks zero, four, and eight. Overall results of the WOMAC questionnaire suggested improvement in the glucosamine treated group (n=45) versus the placebo group (n=53); however, none of the p values were statistically significant. Diary data indicated that the glucosamine group had greater improvement each week while the placebo group had improvement only in the week following their interaction with research staff. Knee examination data for the glucosamine group indicated improvement versus placebo beginning week 4. Adverse effects were about the same in each group (12%) and consisted of mild gastrointestinal symptoms, such as gas, abdominal bloating, and/or cramps. During the open label phase, all participants (n=83) took glucosamine and 77% continued thereafter (Houpt et al, 1999).

- **D. TEMPOROMANDIBULAR JOINT DISORDER**

- **1. OVERVIEW :**

EFFICACY: Adult, possibly effective

DOCUMENTATION: Adult, fair

- **2. SUMMARY :**

- The combination of glucosamine hydrochloride and chondroitin sulfate decreased the sounds associated with temporomandibular joint (TMJ) disorder and may decrease TMJ pain and swelling
- The use of glucosamine hydrochloride and chondroitin sulfate may decrease the amount of over-the-counter medications required for pain

relief

- 3. **ADULT :**
 - a. Decreased temporomandibular joint (TMJ) tenderness and TMJ sounds and fewer over-the-counter analgesics occurred with supplementation with glucosamine and chondroitin in a 12-week, double-blind, placebo-controlled study. Patients received 750 milligrams (mg) glucosamine hydrochloride twice daily and 600 mg chondroitin sulfate twice daily (n=23) or placebo (n=22). Due to dropouts and patients lost to follow-up, 14 patients completed the trial in the treatment group and 20 patients in the placebo group. Statistically significant improvements were demonstrated in one scale of the McGill Pain Questionnaire in the treatment group (evaluative pain rating index (p=0.03)) and four scales in the placebo group (sensory (p=0.03), evaluative (p=0.01), number of words (p=0.03), and miscellaneous (p=0.01) pain rating indices). There was also a significant decrease in the visual analog scale in the placebo group (p=0.01). TMJ noises significantly decreased in the treatment group from 11 patients with sounds to 8 (p less than 0.05), with no change in any patient in the control group. The mean number of over-the-counter medications (mainly acetaminophen) was significantly fewer in the treatment group (p=0.03). Adverse effects were mainly gastrointestinal, resolved spontaneously, and were reported as transient (Nguyen et al, 2001).
 - b. Administration of 1600 milligrams (mg), glucosamine hydrochloride, a 1200 mg mixture of chondroitin sulfate-4 and -6, and 1000 mg calcium ascorbate, all taken twice daily, produced beneficial effects in temporomandibular joint (TMJ) arthritis. Of the 50 participants in an uncontrolled, preliminary study, 80% reported decreased joint noises; 2% reported a worsening in symptoms of pain and/or swelling; 10% failed to comply with conditions of the study, and 8% reported no change. Several (actual number not reported) of the 40 patients that noted a decrease in joint noises also reported a decrease in pain and swelling in the TMJ, as well as other joints. Responses were noted an average of 14 to 21 days after starting treatment; however, patients were allowed to take aspirin and ibuprofen when TMJ pain interfered with daily activities. Two individuals reported gastrointestinal upset that subsided on treatment cessation (Shankland, 1998).

4.6 COMPARATIVE EFFICACY

- **A. IBUPROFEN**
 - 1. **SUMMARY :**
 - a. Glucosamine is at least as effective as ibuprofen in the treatment of osteoarthritis, including osteoarthritis in the temporomandibular joint (TMJ). Glucosamine may demonstrate a slower onset of action.
 - 2. **OSTEOARTHRITIS :**
 - a. Oral glucosamine sulfate was reported to be at least as effective as oral ibuprofen after eight weeks of treatment in one study involving 40 patients with osteoarthritis of the knee. Treatment with glucosamine sulphate 1500

milligrams or ibuprofen 1200 milligrams daily in three divided doses was assigned in a randomized and double-blind fashion. Articular pain, swelling, and general symptoms were evaluated at regular intervals. At the end of the trial, the examining physician gave an opinion of overall efficacy of treatment as "good," "fair," or "insufficient." Pain scores decreased significantly in both groups but the onset of action was more rapid with ibuprofen, with maximum effectiveness reached after 2 weeks, whereas glucosamine was associated with a gradual, progressive improvement throughout the trial. At week 8, a "good" response was observed in 44% and 15% of patients receiving glucosamine and ibuprofen, respectively ($p=0.04$ for differences between treatments) (Vaz, 1982).

- b. In a randomized, double-blind, parallel-group study, glucosamine 500 milligrams (mg) orally three times daily was as effective as ibuprofen 400 mg three times daily for four weeks in the treatment of 200 inpatients with osteoarthritis (OA) of the knee (Mueller-Fassbender et al, 1994). Enrollment criteria included a Lequesne index score of seven or greater, presence of OA for at least three months, and lack of concomitant OA therapy. Treatment success, defined as a decrease in Lequesne index score of at least 2 points (if baseline was greater than 12) or 1 point (if baseline was 12 or less) and a clinician rating of at least "good," occurred in 48% of glucosamine patients and 52% of ibuprofen patients by study end (no significant difference). The average Lequesne score for both groups decreased from approximately 16 to 9.6 after four weeks. Therapeutic effect was generally obtained sooner with ibuprofen but glucosamine was significantly better tolerated (p less than 0.01) than ibuprofen: six patients reported adverse effects (versus 35 with ibuprofen) and one discontinued treatment (versus seven with ibuprofen). The definition of treatment response as well as the short duration of the study leave the results open to debate as to their clinical significance.
- **3. TEMPOROMANDIBULAR JOINT DISORDER**
 - a. Both glucosamine and ibuprofen reduced pain associated with temporomandibular joint (TMJ) osteoarthritis. In a 3-month evaluation, patients with radiographic evidence of degenerative joint disease and TMJ pain on function were randomized to receive glucosamine sulfate (GS) 500 milligrams (mg) 3 times daily ($n=21$) or ibuprofen 400 mg 3 times daily ($n=18$) in a double-blind manner. Patients were also assessed 1 month after discontinuation of treatment medication. The primary outcome measure was a 20% reduction in TMJ pain. The number of patients with this clinical response did not differ between the groups (71% of patients with glucosamine sulfate ($n=15$) and 61% with ibuprofen ($n=11$), $p=0.73$). There were significant decreases in all pain measures in each group as compared to baseline values (all reported p values less than 0.016). There was no difference in acetaminophen use compared to baseline usage during the treatment phase of the trial; however, the amount of acetaminophen used from days 90 to 120 was significantly less

in the GS group ($p=0.009$), suggesting a carryover effect of glucosamine sulfate. Three patients who received ibuprofen and one patient treated with GS dropped out due to stomach upset. Inadequate control of pain in the ibuprofen group resulted in one dropout, as did dizziness in the GS group. No adverse effects were reported in the 39 patients who completed the trial (Thie et al, 2001).

- **B. PIROXICAM**

- 1. **SUMMARY :**

- a. Glucosamine is at least as effective as piroxicam in the treatment of osteoarthritis. Glucosamine may demonstrate a slower onset of action.

- 2. **OSTEOARTHRITIS :**

- a. Glucosamine sulfate was as effective as piroxicam alone or a combination of glucosamine and piroxicam in a randomized, multicenter, double-blind, placebo-controlled trial. Subjects ($n=329$) received either glucosamine sulfate 1500 milligrams (mg) daily, piroxicam 20 mg daily, a combination of glucosamine and piroxicam, or placebo for 60 days, followed by a 60-day observation period without treatment. Treatment outcome evaluated with the Lequesne index demonstrated significant ($p=0.0001$) treatment effects, time effects, and treatment-time interactions for all treatments compared to placebo. Glucosamine appeared to have a persistent treatment effect after withdrawal compared to piroxicam. Significantly fewer adverse effects were recorded for glucosamine ($p=0.0001$) (Rovati et al, 1994).

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