Firstmed Pharma

Flexost

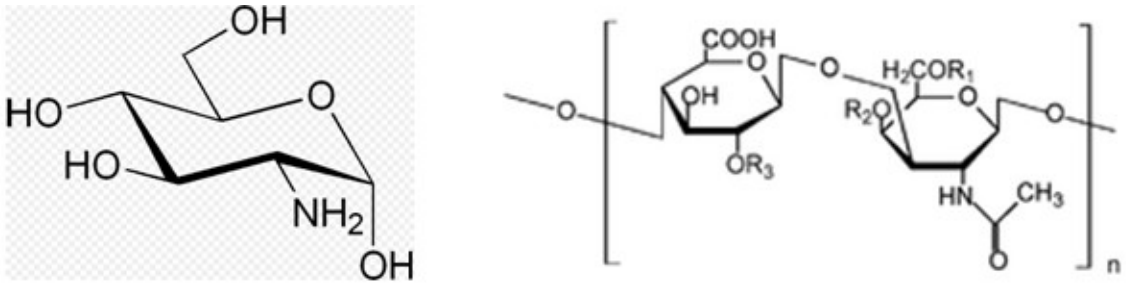
Dietary Supplement
Joint Repair Formula

CAPSULES

OTC

DESCRIPTION

FLEXOST is indicated for the treatment and prevention of osteoarthritis. Its composition is formulated from natural products Glucosamine sulfate 220mg, chondroitin 220mg.



FLEXOST is white to off-white powder (60 mesh) with a solubility of 2.5mg/ml in pH 5.2 water. Each FLEXOST capsule contains 440mg of the formulated natural components. Each capsule shell contains gelatin, titanium dioxide and FD&C Blue top white base No. 1.

CLINICAL PHARMACOLOGY

Mechanism of Action

The benefit of Flexost in patients with osteoarthritis is the result of a number of effects including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans,[1] and the decrease in catabolic activity of chondrocytes inhibiting the synthesis of proteolytic enzymes and other substances that contribute to damage cartilage matrix and cause death of articular chondrocytes

Pharmacokinetics

Absorption

FLEXOST well absorbed from an oral dose, with about 90 percent gets absorbed in the small intestine, and from there it is transported via the portal circulation to the liver. Significant fraction of the ingested glucosamine is catabolized by the first/pass metabolism in the liver. Free glucosamine is not detected in the serum after oral intake, and it is not know how much of the ingested dose is take up in the joints in humans. Some uptake in articular cartilage is seen in human studies. After oral administration, glucosamine is rapidly absorbed so that some samples

taken five and ten minutes after administration contained the highest observed concentrations as compared with the remaining samples (fig 1). The oral doses, however, were only 21% bioavailable.

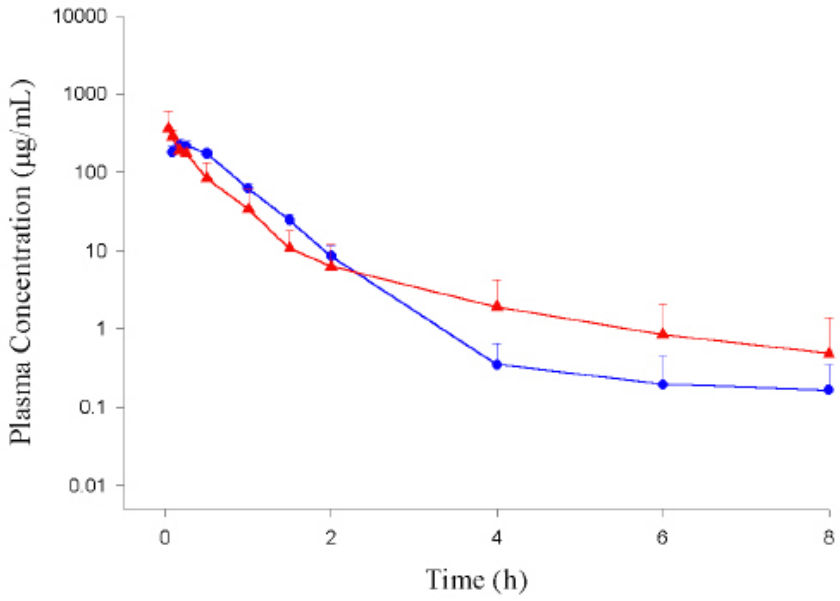


Figure 1: Mean glucosamine plasma concentrations versus time curve after a single i.v. bolus (□) and i.p. (□) administration of 350mg kg -1 glucosamine HCl to rats. Concentrations below 1.23 mg/mL were not used in the calculation of pharmacokinetic parameters. Error bars represent standard deviation of the mean (n=5 for i.v. and 6 for i.p.).

The rate and extent of absorption of FLEXOST are not influenced by food; thus FLEXOST may be taken with or without food.

Distribution

The mean apparent volume of distribution following oral administration is approximately 52 L, indicating that FLEXOST is distributed into tissues. At therapeutic concentrations, 94% of FLEXOST in plasma is bound to proteins. In which radioactivity rapidly appears in liver, kidneys and other tissues, including the articular cartilage.

Metabolism

FLEXOST is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination

Following a single dose of 440mg FLEXOST in normal weight and obese subjects, fecal and urine excretion of the unabsorbed product was found to be the major route of elimination.

Glucosamine is rapidly eliminated so that for most samples, the plasma concentration falls below the detectable level of 0.63 $g.mL^{-1}$ in 6 h, post-dose (fig 2).

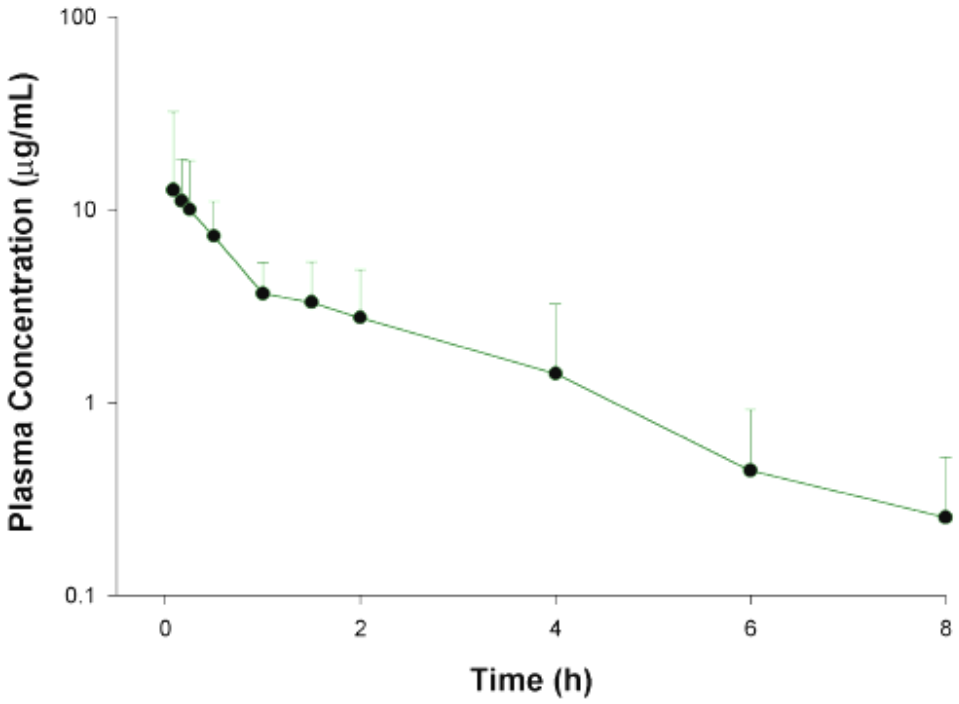


Figure 2: Mean glucosamine plasma concentrations versus time curve after a single oral administration of 350mg.kg- *1* glucosamine HCl to rats. Concentrations below 1.23 mg/mL were not used in the calculation of pharmacokinetic parameters. Error bars represent standard deviation of the mean (n=5).

After a single dose of 440 mg CGS traced with 14C-Gl, radioactivity appeared incorporated in plasma globulins with a lag time of 1.5 h and increasing with a rate of 0.24 h-1. The peak was reached at the 9th h after administration. The radioactivity then was eliminated with a t1/2 of 58 h. The absolute oral bioavailability evaluated on the AUCs of the globulin-incorporated radioactivity was 44%. The fecal excretion in 120 h was 11.3% of the administered dose showing that at least 88.7% of the administered dose was absorbed through the gastrointestinal tract.

Special Populations

Geriatrics: In studies no difference has been experienced on geriatrics then normal adult population.

Pediatrics: FLEXOST has not been evaluated in individuals less than 16 years old.

Patients with Diabetes Mellitus: In male patients with diabetes mellitus after a 420 mg FLEXOST dose, While there have been concerns originating from in vitro studies and intravenous

administration to rodents that glucosamine might adversely affect glucose metabolism, careful studies in humans show no adverse effects on glucose homeostasis. Overall, 16 studies including 854 subjects for 37 weeks reported no adverse effects on glucose metabolism. Glucosamine is well tolerated by humans for periods of up to three years. While the usual dose is 1500 mg/day in three doses, doses of up to 3200 mg/day were well tolerated. Healthy young subjects had no adverse effects from infusion of 9.7 g and only one of five developed a headache when 30.5 g was infused. This suggests that humans tolerate intake of at least 184 mg/kg/day of glucosamine daily. In 13 clinical trials reporting safety information there were no adverse effects of glucosamine on blood chemistries, hematologic parameters, urinalysis, occult blood in feces, or cardiovascular parameters. Symptoms or side effects were reported significantly less frequently with glucosamine than with placebo. (See Case Studies)
No dose adjustment is warranted

DRUG-DRUG INTERACTIONS

None known

CLINICAL STUDIES

The efficacy and safety of FLEXOST in the treatment and prevention of osteoarthritis has been evaluated in 22 clinical trials (see table 1) of up to 36-month duration, involving over 6500 patients. FLEXOST , when taken as needed up to three times per day, was shown to be effective in improving joint space narrowing which is the prime indicator of arthritic joint damage and inhibiting progression of degenerative cartilage lesions. Clinical studies also showed significantly superior to placebo and superior to ibuprofen.

Table 1 Clinical trial summary

Human clinical trial summary

Study	Type study	Glucosamine form	Other treatment	Route*	Dose mg/d	No. of subjects	Duration days
Almada et al. (2000)	RCT	SO_4	None	Oral	1500	6	84
Braham et al. (2003)	RCT	HCl	None	Oral	2000	25	84
D'Ambrosio et al. (1981)	RCT	SO_4	None	Oral/iv/im	1500	15	21
Das and Hammad (2000)	RCT	HCl	CHS	Oral	2000	46	192
Drovanti et al. (1980)	RCT	SO_4	None	Oral	1500	40	30
Forster et al. (1996)	RCT	SO_4	None	Oral	1500	78	90
Giordano et al. (1996)	Observational	SO_4	None	Oral	1500	20	365
Houpt et al. (1999)	RCT	HCl	None	Oral	1500	45	147
Hughes and Carr (2002)	RCT	SO_4	None	Oral	1500	39	168
Leffler et al. (1999)	RCT	HCl	CHS, Mn	Oral	1500	31	112
Muller-Fabbender et al. (1994)	RCT-C	SO_4	Vs. ibuprofen	Oral	1500	100	28
Mund-Hoym (1980)	Controlled	SO_4	Vs. phenylbutazone	Oral/im	1000	40	32
Murad and Tabibian (2001)	Controlled	SO_4	Supplement	Oral	Uncert	57	35
Nguyen et al. (2003)	RCT	HCl	CHS	Oral	1500	19	84
Noack et al. (1994)	RCT	SO_4	None	Oral	1500	120	28
Pavelka et al. (2002)	RCT	SO_4	None	Oral	1500	84	1095
Pujalte et al. (1980)	RCT	SO_4	None	Oral	1500	11	49
Qui et al. (1998)	RCT-C	SO_4	Vs. ibuprofen	Oral	1500	88	28
Reicheit et al. (1994)	RCT	SO_4	None	IM	114	73	42
Reginster et al. (2001)	RCT	SO_4	None	Oral	1500	87	1095
Rindone et al. (2000)	RCT	SO_4	None	Oral	1500	49	60
Rovati (1997)	RCT-P-C	SO_4	Vs. piroxicam	Oral	1500	80	150
Rovati (1992), study 1	RCT	SO_4	None	Oral	1500	123	28
Rovati (1992), study 2	RCT	SO_4	None	Oral	1500	76	42
Rovati (1992), study 3	RCT-C	SO_4	Vs. ibuprofen	Oral	1500	100	28
Scroggie et al. (2003)	RCT	HCl	CHS	Oral	1500	22	90
Shankland (1998)	Observational	HCl	CHS	Oral	3200	50	35
Tannis et al. (2004)	RCT	SO_4	None	Oral	1500	11	84
Tapadinhas et al. (1982)	Observational	SO_4	None	Oral	1500	1367	50
Thie et al. (2001)	RCT-C	SO_4	Vs. ibuprofen	Oral	1500	22	90
Yu et al. (2003)	Observational	SO_4	None	Oral	1500	12	28
Vajranetra (1984)	Observational	SO_4	None	Oral/ia	1500	108	84
Vas (1982)	RCT-C	SO_4	Vs. ibuprofen	Oral	1500	19	56

Abbreviations: RCT, randomized controlled trial; C, comparator; P, placebo; CHS, chondrotin sulfate; iv, intravenous; im, intramuscular; ia, intraarticular.

The efficacy of glucosamine for arthritic complaints has been extensively studied and three recent meta-analyses (McAlindon et al., 2000; Richy et al., 2003; Towheed et al., 2004) that critically review randomized controlled trials (RCTs) are available. McAlindon et al. (2000) conclude that glucosamine was moderately efficacious for relief of arthritic complaints. Richy et al. (2003) conclude that glucosamine had highly significant efficacy on all aspects of knee osteoarthritis including joint space narrowing, pain, and mobility scores. Towheed et al. (2004) report that ''In the 13 RCTs in which glucosamine was compared to placebo, glucosamine was found to be superior in all RCTs, except one. In the four RCTs in which glucosamine was compared to an NSAID, glucosamine was superior in two and equivalent in two.'' In our current evaluation 23 clinical studies of patients with osteoarthritis were reviewed (Table 2); this does not include the three studies of temporo-mandibular joint (TMJ) symptoms.

Twelve studies reported significant differences and included P-values (from 0.05 to 0.001). Seven indicated that significant improvement was seen but did not provide P-values; a P-value of 0.05 was assigned to these studies. Only three studies indicated that no significant difference was seen and two noted a slight improvement with glucosamine administration; a P-value of 0.1 was assigned to these studies since they reported favorable but not quite statistically significant results. The average of all reported and imputed P-values for the 22 studies was 0.040 and the median P-value was 0.05. While a detailed analysis of efficacy was not undertaken, this survey indicates that glucosamine administration, at a dose of 1500 mg/day, is moderately effective in decreasing arthritic complaints.

Table 2 Clinical trial on efficacy of Glucosamine for arthritic complaints.

Study	Joints evaluated	Arthritis symptoms significant difference
Braham et al. (2003)	Knees	0.038
D'Ambrosio et al. (1981)	Generalized OA	0.01
Das and Hammad (2000)	Knees	0.04
Drovanti et al. (1980)	Generalized OA	0.005
Forster et al. (1996)	Knees	Sign. diff. (0.05)
Giordano et al. (1996)	Generalized OA	0.001
Houpt et al. (1999)	Knees	NCS (0.1)
Hughes and Carr (2002)	Knees	NCS (0.1)
Leffler et al. (1999)	Knees or back	0.02
Muller-Fabbender et al. (1994)	Knees	Sign. diff. (0.05)
Mund-Hoym (1980)	Back	Sign. diff. (0.05)
Noack et al. (1994)	Knees	0.05
Pavelka et al. (2002)	Knees	0.01
Pujalte et al. (1980)	Generalized OA	0.01
Qui et al. (1998)	Knees	Sign. diff. (0.05)
Reicheit et al. (1994)	Knees	Sign. diff. (0.05)
Reginster et al. (2001)	Knees	Sign. diff. (0.05)
Rindone et al. (2000)	Knees	NCS (0.1)
Rovati (1997)	Knees	Sign. diff. (0.05)
Rovati (1992), study 1	Knees	0.014
Rovati (1992), study 2	Knees	0.012
Tapadinhas et al. (1982)	Generalized OA	0.001
Vajranetra (1984)	Knees	Sign. diff. (0.05)

Abbreviations: NA, not applicable; OA, osteoarthritis; NA, not available; NCS, not clinically significant.

Objective measures of safety

In two metabolic ward studies, volunteers have received large doses of glucosamine intravenously over 300 min. Pouwels et al. (2001) intravenously infused _7.2 g of glucosamine as the sulfate salt over a 300 min period into 10 healthy volunteers. This was well tolerated and not associated with reported side effects. Monauni et al. (2000) intravenously infused 9.7 g of glucosamine over a 300 min period into 10 healthy volunteers. Again this was well tolerated with no reported side effects. When they subsequently intravenously infused 30.5 g of glucosamine—achieving plasma levels >20-fold higher than would be expected with usual doses of oral glucosamine—into five healthy volunteers, this dose was well tolerated by four subjects and only one had symptoms—he developed a headache. Thirteen studies reported specific safety measures including some of these assessments: chemistry panel including liver and kidney safety assessments, hematologic values (white blood count, red blood count, hemoglobin, and platelet count), urinalyses, occult blood measurements of stool, and cardiovascular parameters including blood pressure and pulse rate (Table 3). None of the studies reported adverse effects on these measurements from glucosamine administration. In general these safety reports included >800 subjects treated for a weighted average of _40 weeks. Specifically the number of studies assessing various parameters were as follows: chemistry panel, 12; hematologic parameters, 13; urinalyses, 10; occult blood in stool, 3; and cardiovascular parameters, 6. Blood pressure and pulse rate were monitored continuously for the 21 subjects who had large amounts of glucosamine infused intravenously with no reported adverse effects (Monauni et al., 2000; Pouwels et al., 2001). None of the studies reported significant changes in these parameters.

Table 3 Evaluation of fasting plasma glucose and safety parameters.

Evaluation of fasting plasma glucose and safety parameters

Study	Glucose before	mg/dl after	Summary	Blood chem	CBC	UA	Occult blood	BP P	Side effects GluN/P
Almada et al. (2000)	94	94		NA	NA	NA	NA	NA	NA
Braham et al. (2003)	NA			NA	NA	NA	NA	NA	1.10
D'Ambrosio et al. (1981)	109	97		NCS	NCS	NCS	NA	NCS	1.00
Das and Hammad (2000)	NA			NA	NA	NA	NA	NA	0.89
Drovanti et al. (1980)	82	82		NCS	NCS	NA	NCS	NA	0.83
Forster et al. (1996)	NA			NA	NA	NA	NA	NA	0.20
Giordano et al. (1996)	NCS			NCS	NCS	NCS	NA	NA	1.00
Houpt et al. (1999)	NA			NA	NA	NA	NA	NA	1.00
Hughes and Carr (2002)	NCS			NCS	NCS	NCS	NA	NA	0.90
Leffler et al. (1999)	NA			NA	NCS	NA	NCS	NCS	0.97
Muller-Fabbender et al. (1994)	NA			NA	NA	NA	NA	NCS	NA
Nguyen et al. (2003)	NA			NA	NA	NA	NA	NA	1.43
Noack et al. (1994)	NCS			NCS	NCS	NCS	NA	NCS	0.62
Pavelka et al. (2002)	NCS			NCS	NCS	NCS	NA	NA	0.56
Pujalte et al. (1980)	NA			NCS	NCS	NCS	NA	NA	0.00
Qui et al. (1998)	NA			NCS	NCS	NCS	NA	NA	NA
Reginster et al. (2001)	Slightly lower			NCS	NCS	NCS	NA	NCS	0.82
Rindone et al. (2000)	NA			NA	NA	NA	NA	NA	0.50
Rovati (1997)	NA			NA	NA	NA	NA	NA	0.62
Rovati (1992), study 1	NA			NCS	NCS	NCS	NA	NA	0.62
Rovati (1992), study 2	NA			NCS	NCS	NCS	NA	NA	0.71
Rovati (1992), study 3	NA			NCS	NCS	NCS	NA	NA	NA
Scroggie et al. (2003)	HbA1c	NCS		NA	NA	NA	NA	NA	NA
Tannis et al. (2004)	82.3	79.2		NA	NA	NA	NA	NA	NA
Yu et al. (2003)	97.2	97.2		NA	NA	NA	NA	NA	NA
Vas (1982)	NA			NA	NCS	NA	NCS	NCS	NA
Average	92.9	89.9							0.76
No. with reports		5	16	12	13	10	3	6	18
Total patients		84	854	803	826	736	90	372	988
Weighted average no. of weeks		5.6	37.2	38.9	38.6	41.7	9.1	40.7	37.2

Abbreviations: NA, not available; NCS, not clinically significant; HbA1c, glycosylated hemoglobin; chem., chemistry; UA, urinalysis; occult blood, stool measurement; BP, blood pressure; P, pulse; GlucN/P, ratio of side effects from glucosamine divided by those from placebo.

INDICATIONS AND USAGE

FLEXOST is indicated for the treatment and prevention of osteoarthritis.

CONTRAINDICATIONS

Hypersensitivity to active components.

Patients taken medication for diabetes mellitus and overweight may have problems with glucose tolerance should have their blood sugars carefully monitored. Even though case studies conducted on patients with DB2 have not encountered significant blood sugar level changes(see case studies).

WARNINGS

In most human studies, glucosamine sulfate has been well tolerated for 30 to 160 days.

Side effects may include upset stomach, drowsiness, insomnia, headache, skin reactions, sun sensitivity, and nail toughening. There are rare reports of abdominal pain, loss of appetite, vomiting, nausea, flatulence (gas), constipation, heartburn, and diarrhea. Based on several human cases, temporary increases in blood pressure and heart rate, as well as palpitations, may occur with glucosamine/chondroitin products. Based on animal research, glucosamine theoretically may increase the risk for eye cataract formation.

PRECAUTIONS

Allergies

Since glucosamine can be made from the shells of shrimp, crab, and other shellfish, people with shellfish allergy or iodine hypersensitivity may have an allergic reaction to glucosamine products. However, some research suggests that there is not enough shrimp allergen in glucosamine supplements to trigger reactions in patients who are allergic to shrimp. Nevertheless, caution is warranted. A serious hypersensitivity reaction including throat swelling has been reported with glucosamine sulfate. There are reported cases suggesting a link between glucosamine/chondroitin products and asthma exacerbations.

MISUSE POTENTIAL

No potential for misuse has been experienced in pre marketing clinical studies or during post marketing events.

USE IN SPECIAL POPULATIONS

Pregnancy

No adequate and well controlled studies with FLEXOST have been conducted in pregnant women. Because animal reproductive studies are not always predicative of human response FLEXOST during pregnancy is not recommended.

Nursing Mothers

It is not known if FLEXOST is secretes in human milk. Therefore, FLEXOST should not be taken by nursing women.

Pediatric Use

FLEXOST has not been studied in pediatric patients below the age of 16 years. There is not enough scientific evidence to recommend the use of glucosamine in children.

Geriatric Use

Clinical studies of FLEXOST included significant number of patients aged 65 years and older which determined the resonance was similar to younger patients.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. When taken as recommended in the placebo-controlled clinical trials, the following adverse events were reported (see Table 6) for FLEXOST for use as needed:

Table 2 Adverse reactions during clinical studies.

		Flexost 440 mg *		
Adverse Event	Placebo (N=820)	2 capsules /day (N=1400)	3 capsules /day (N=853)	4 capsules /day g (N=472)
Dyspepsia	4%	6%	7%	5%
Drowsiness	2%	2%	2%	3%
Headache	3%	5%	6%	6%
Insomnia	1%	3%	4%	5%
Abdominal pain	3%	3%	3%	4%
Nausea	1%	1%	1%	1%
Loss os appetite	2%	2%	2%	4%
Vomitting	1%	1%	3%	3%

*2 caps per day trial 120 days, 3 and 4 caps per day 90 day trial

Side effects may include Dyspepsia, drowsiness, insomnia, headache. There are rare reports of abdominal pain, loss of appetite, vomiting, and nausea.

Common symptoms with placebo, glucosamine and NSAID

Nonspecific symptoms are commonly reported in clinical trials. In a 3-year study, 93% of subjects receiving placebo reported symptoms (Reginster et al., 2001). The most common symptoms reported with placebo or glucosamine were: mild gastrointestinal symptoms including constipation, diarrhea, nausea, dyspepsia, excessive gas, abdominal distension, and abdominal cramps; headache; and skin rash or pruritis. Eighteen chronic studies that provided side effect data comparing glucosamine to placebo were analyzed (Table 3). The contents of the placebo capsules used in these studies were: not stated, in 9 studies; lactose, in 3; excipients, in 3; inert material, in 1; calcium carbonate, in 1; and 50% maltodextrin and 50% whey protein, in 1. These studies included 988 subjects followed for a weighted average of 37 weeks. In 13 of the 18 studies, symptoms were reported less commonly in glucosamine-treated subjects than in placebo-treated subjects. The ratio of symptoms for glucosamine compared to those for placebo is presented for each study. The placebo has a score of 1.0 and the frequency of symptoms with glucosamine is a fraction of this. When the frequency of symptoms is the same the ratio for glucosamine is 1.0. When less symptoms are reported for glucosamine than placebo, the ratio is less than 1.0. Only two studies reported that symptoms were more common with glucosamine than placebo.

The frequency of symptoms with glucosamine ranged from none (0.0) to 143% (1.43) of those reported for placebo. The average for the ratio of symptoms for glucosamine compared to placebo was 0.76 (95% confidence interval, 0.61–0.92). This suggests that symptoms were 24% less common with glucosamine than placebo and that this was statistically significant. Richy et al. (2003), in their meta-analysis, indicated that the adverse effect rate with glucosamine was 20% lower than placebo. The Institute of Medicine Report (2004) summarizes case reports and other adverse events occurring with glucosamine use. This report concludes that: ‘‘Human studies show an equal incidence of mild, transient adverse effects in placebo control groups and glucosamine groups.’’ (p. 4, 2004) Five studies compared side effects of glucosamine with ibuprofen, the most commonly used non-steroidal anti-inflammatory drug (NSAID) for arthritis. The prevalence of side effects in patients using glucosamine was 10.0% compared to 32.5% for patients using ibuprofen. The Institute of Medicine (2004) report also concluded that side effects were less common with glucosamine than with ibuprofen.

OVERDOSAGE

Single doses up to 7 grams have not presented any more adverse events then normal dosages. From clinical studies the likelihood of overdosing is unknown and unlikely.

DOSAGE AND ADMINISTRATION

FLEXOST recommended starting dose of 2 capsules per day and may be increased up to 5 capsules depending on the level of inflammation and progression of joint space narrowing.

Use with Food

FLEXOST may be taken without regard to food. The safety and effectiveness of FLEXOST beyond 4 years have not been determined at this time.

USE IN SPECIAL POPULATIONS

Geriatrics

No dose adjustment is required in patients >65 years of age.

HOW SUPPLIED

FLEXOST is a dark –blue hard-gelatin capsule containing powder.
FLEXOST 440 mg capsules: Dark –blue two piece No. 0 opaque hard –gelatin capsule. – Bottle containing 120 capsules.

Storage Conditions

Store at 25°C (77°F) excursions permitted to 15° to 30°C (59° to 86°F) Keep bottle tightly closed.

FLEXOST should not be used after the given expiration date stamped on the top of the lid of each bottle.

Distributed by:

Firstmed Pharma, Inc
Division of Firstmed Holding Corporation
Dothan, AL 36301

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Revised May 2007