ARTHROCEN 300 MG- avocado/soy unsaponifiables capsule
Pharmin USA, LLC

ARTHROCEN 300 mg

ARTHROCEN 300 MG- Avocado/Soy Unsaponifiables (ASU) Pharmin USA, LLC
HIGHLIGHTS OF PRESCRIBING INFORMATION
DIETARY SUPPLEMENT
Arthrocen is classified as a dietary supplement in the US, however, in some other countries it is categorized as a prescription drug.

1 INDICATION AND USAGE

Rheumatology: Arthrocen 300 mg Capsules is indicated to treat connective tissues in osteoarthritis and prevent cartilage degradations.

Dentistry: Arthrocen Capsules is indicated to treat periodontitis.

2 DOSAGE AND ADMINISTATION

The recommended dose of Arthrocen Capsules for adult is one capsule a day preferably with a meal. It may take up to 3 to 6 months for desired effects.

3 DOSAGE FORMS AND STRENGHTS

Capsules: 300 mg avocado/soy unsaponifiables per capsule.

4 CONTRAINDICATIONS

History of hypersensitivity to soy or any of the product components.

5 WARNINGS AND PRECAUTIONS

This product has been prescribed for a particular condition, therefore, this medicine should not be used for other conditions. Do not give this medicine to anyone else. Keep this and all medicines out of the reach of children. This medicine should not be used after the expiration date. This product is presented in capsules made of hard gelatin.

6 ADVERSE REACTIONS

Infrequent: in some patients, it may cause stomach upset. To avoid this discomfort capsules should be taken with meals.

Rare: hypersensitivity to soy or any of the product components.

7 Preclinical and Clinical Trail Experience

Chondroprotective, anabolic, and anticatabolic effects of Avocado/Soy Unsaponifiables have been demonstrated in several studies of Avocado/Soy Unsaponifiables solid dosage form.

A- Human Clinical Studies
The efficacy and safety of Arthrocen, avocado/soybean unsaponifiables, with that of placebo assessed in treatment of patients with knee osteoarthritis (OA). Research indicated a significant difference was demonstrated between the daily dose of Arthrocen 300 mg and placebo after 9 months of follow-up, patients treated with Arthrcoen 300 mg were significantly improved compared to placebo in terms of LI (<0.001) and VAS (P < 0.01). Daily amount of analgesics reduced significantly from baseline 67% to 12.2% at the final visit. This study suggests that a daily administration of 300 mg oral Arthrocen allows a significant clinical improvement compared to placebo after 6 months relieving joint stiffness, pain as well as enhancing ability to conduct daily functions with reduction in analgesics' intakes.

Further four double-blind placebo-controlled randomized trials (*Appelboom et al.; Blotman et al.; Lequesne et al.; Maheu et al.*), a meta-analysis (*Christensen et al.*), and two systematic reviews (*Ameye and Chee ; Ernst*) evaluated the effects of ASUs on knee and hip OA. As for safety, none of the four trials reported adverse effects of ASU when 300 - 600mg ASU/day was administered for 3 months to 2 years (mean age of subjects 62-65 y).

B- Animal Study
Goudarzi et al showed Arthrocen can reduce joint pain in OA animal model. OA was induced in male Wistar rats by intra-articular injection of sodium monoiodoacetate (MIA: 0.3mg) and animals were allowed to recover for 14 days. Arthrocen was added to the drinking water which was available to

animals ad libitum. On day 30, joint pain was assessed by dynamic incapacitance while referred pain was determined by von Frey hair algesiometry.

The joint damage induced by MIA injection was severe and was consistent with end-stage OA. Arthrocen consumption (approximately 35 mg/day) attenuated the joint oedema associated with MIA injection. Hindlimb weight bearing also significantly improved in Arthrocen-treated rats ($P<0.05$); however, von Frey hair mechanosensitivity was unaffected by this treatment. These data indicate that Arthrocen has the potential to reduce joint inflammation and pain associated with end-stage OA. No adverse effects were noted.

Preclinical Trail Experience

A*-Goudarzi et al* found a role for Arthrocen in attenuating the inflammatory response both at the protein and mRNA level. Furthermore, Arthrocen diminished prostaglandin E2 (PGE2) levelsin response to an inflammatory trigger. Unlike traditional COX-2 inhibitors, this response rather specifically attenuated PGE2 levels in the presence of inflammation and without lowering levels of other eicosanoids. This implies that Arthrocen could potentially bring about the reduced pain produced by COX-2 inhibitors without the known side effects of COX-2 inhibition.

B*- Taylor et al* found a role for Arthrocen in attenuating the inflammatory response at the mRNA level while inducing significant changes in numerous cytokines. They discovered that while Arthrocen alone did not increase IL-8 or MCP1 levels, its presence had a synergistic effect on the observed increase in response to LPS stimulation. Additionally, this synergistic effect of Arthrocen on LPS stimulation of IL-8 and MCP1 protein levels was also observed at the mRNA level and suggests a regulatory mechanism at the transcriptional level. Interestingly, Arthrocen induced no changes in any of the eicosanoids studied. This multi-omics approach implies that Arthrocen functions at the level of gene transcription to attenuate inflammation mediated by monocytes in OA.

8 Post Marketing Experience

Since side effects are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure. The following adverse effect identified during post-approval of avocado soy usaponifiables: *nausea and stomach upset*

9 DRUG INTERACTION:

Severe interactions were not reported. Nevertheless, to avoid interactions with other drugs, the patient shall inform the physician if she/he is taking another medicine.

10 USE IN SPECIFIC POPULATION

10.1 Pregnancy

There is not available data to evaluate teratogenic or fetotoxic effects, therefore, it should not be used during pregnancy and breastfeeding. Therefore, not recommended during pregnancy.

10.2 Labor and Delivery

The effects of avocado soy Unsaponifiables on labor and delivery are unknown.

Therefore, not recommended during labor.

10.3 Nursing Mothers

The effects of avocado soy Unsaponifiables on nursing mother are unknown.

Therefore, not recommended during lactation.

11 OVER DOSAGE: None reported.

12 Effects on ability to drive and use machines: None reported.

13. DESCRIPTION

Arthrocen 300 mg Capsules:

Avocado/Soy Unsaponifiables (A1S2U)

- ***Unsaponifiable of Avocado 100 mg (1 part)***
- ***Unsaponifiable of Soybean 200 mg (2 parts)***

ASU is an anti-osteoarthritic agent that has been derived from the unsaponifiable residues of avocado and soybean, and mixed in a ratio of 1:2 respectively. It has been suggested that its phytosterol components are responsible for up-regulation of glycosaminoglycan and collagen synthesis and reduction of pro inflammatory mediators. The synergistic activity between avocado and soybean, and their relative ratios, has been found to be significantly effective.

The major components of ASU by weight are the phytosterols, such as beta-sitosterol, campesterol and

stigmasterol. Other components of ASU include fat-soluble vitamins, triterpene alcohols and possibly furan fatty acids.

14. CLINICAL PHARMACOLOGY

ASU possesses chondroprotective, anabolic, and anticatabolic properties. It inhibits the breakdown of cartilage and promotes cartilage repair by inhibiting a number of molecules and pathways implicated in osteoarthritis.

14.1 Mechanism of Action:

ASU stimulates the synthesis of collagen and aggrecan by inhibiting inflammatory cytokines such as IL-1, IL-6, IL-8, TNF, and PGE2 through modulation of NF-kappaB. ASU inhibitory affects an array of inflammatory molecules including expression of COX-2 and production of PGE2 in chondrocytes. COX-2 regulates the production of PGE2; both are mediators involved in the process of cartilage breakdown. ASU also inhibits the release and activity of collagenase (MMP2) and stromelysin 1 (MMP3) in cultured chondrocytes increases tissue inhibitors of metalloproteinases (TIMP- 1) and inhibits IL1-induced ERK in chondrocytes in vitro.

14.2 Pharmacokinetics and Distributions:

Phytosterols are primarily eliminated via feces fast, however, remnants may stay up few days in the organs. The absorptions are slightly higher in women than men and can be measured through biliary eliminations.

Researches indicate phytosterols can be distributed fairly similarly in any organs. The adrenal glands, ovaries and intestinal epithelia showing the maximum retention of phytosterols.

15. NONCLINICAL TOXICOLOGY

15.1 Toxicology

There is no ASU toxicological side effects were reported up at the dose of 300 mg a day.

15.2 Carcinogenesis, Mutagenesis, Impairment Of Fertility

No carcinogenicity, mutagenicity, or fertility studies have been conducted with ASU.

HOW SUPPLIED/STORAGE AND HANDLING

Each Arthrocen Capsule, intended for oral administration, is orange-purple bovine zero size capsule.

Each Arthrocen capsule contains 300 mg avocado soy unsaponifiables and are supplied as follows:

NDC 70586-2012-1 Bottles of 60 capsules.
NDC 70586-2012-5 Boxes of 30 capsules in blisters.

Arthrocen possesses various outer display packaging worldwide:

STORAGE:

Store at 20° to 25°C (68° to 77°F) excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

LICENSE HOLDER:

Pharmin USA, LLC
Arthrocen is a registered trademark of Pharmin USA, LLC
US Reg. No: 4397178

Manufactured For:

Pharmin USA, LLC
San Jose, California 95128

United States of America

Address inquiries to Pharmin USA, LLC, info@pharminusa.com, www.pharminusa.com.

Arthrocen is manufactured in GMP and FDA inspected facility in State of California.

Made in USA

Package label principal display panel (30 capsules):

NDC: 70586-2012-5
Barcode No: 982168208057

SWALLOW CAPSULES. DO NOT CHEW.

Consult a physician before using this product or any dietary supplement.

Take one capsule per day.
It may take up to 3 to 6 months for desired effects. Keep out of the reach of children.
Shellfish and Gluten free.

Dairy and flavor Free.
One capsule a day.
Non GMO.

Contain: SOY

S U P P L E M E N T F A C T S

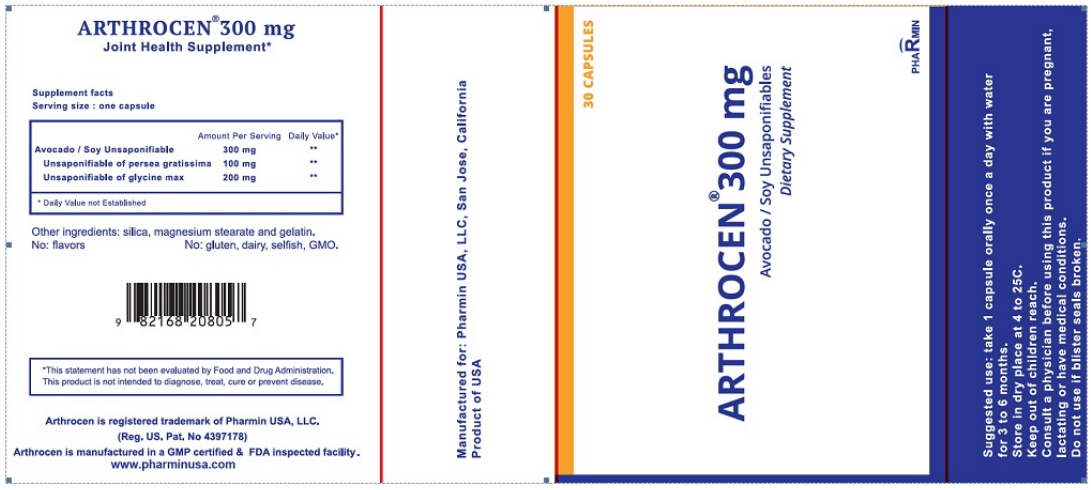
Serving Size: 1 Capsule
Serving Per Container: 30

	Amount Serving	% Daily Value
Avocado/Soy Unsaponifiables	300 mg	*
Avocado Unsaponifiables	1 part	
Soy Unsaponifiables	2 parts	

*Daily value not established

Other ingredients:
Magnesium Stearate, gelatin fines, FD&C #5 colorant, titanium dioxide, mixed tocopherols, soy protein isolate, silicon dioxide, microcrystalline cellulose and acacia gum.

Packaging



ARTHROCEN 300 MG

avocado/soy unsaponifiables capsule

Product Information			
Product Type	DIETARY SUPPLEMENT	**Item Code (Source)**	NHRIC:70586-2012

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AVOCADO OIL UNSAPONIFIABLES (UNII: UID2HJ7GFT) (AVOCADO OIL UNSAPONIFIABLES - UNII:UID2HJ7GFT)	AVOCADO OIL UNSAPONIFIABLES	100 mg
SOYBEAN (UNII: L7HT8F1ZOD) (SOYBEAN - UNII:L7HT8F1ZOD)	SOYBEAN	200 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TOCOPHEROL (UNII: R0ZB2556P8)	
SOY PROTEIN (UNII: R44IWB3RN5)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
ACACIA (UNII: 5C5403N26O)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NHRIC:70586-2012-5	3 in 1 BOX		
1		10 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
dietary supplement		07/08/2007	

Supplement Facts

Serving Size : **Serving per Container :**

Amount Per Serving	% Daily Value
color	
shape	
size (solid drugs) 22 mm	
scoring 1	
imprint	

Labeler - Pharmin USA, LLC (025964216)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmin USA, LLC		025964216	manufacture(70586-2012)

Revised: 8/2017 Pharmin USA, LLC