

Confis ULTRA

**A new era of joint
well-being for dogs**



**Supports joint metabolism
in case of osteoarthritis**

Candioli
PHARMA

THE VICIOUS CIRCLE OF OSTEOARTHRITIS

Evolution and progression of osteoarthritis are due to the combination of the following factors:

- **degeneration**
- **inflammation**
- **oxidative damage**^{7,14,21}

Simultaneous management thereof is the most effective way to act on the articular metabolism and improve the quality of life of the osteoarthritic patient^{2,3,9,23}

**JOINT TRAUMA OR OVERLOAD
INSTABILITY**

SYNOVITIS

1 INFLAMMATION

BLOOD VESSEL
SYNOVIAL MEMBRANE

2 OXIDATIVE STRESS
↑ ROS

• **CHRONIC INFLAMMATION**
• **TISSUE DAMAGE AND REMODELING**
• **OXIDATIVE STRESS**

SYNOVIAL FLUID

Cartilage degradation products

Cartilage cracking

Collagen type II and GAGs degradation

SYNOVITIS

ARTICULAR CARTILAGE

SUBCHONDRAL BONE

Subchondral sclerosis

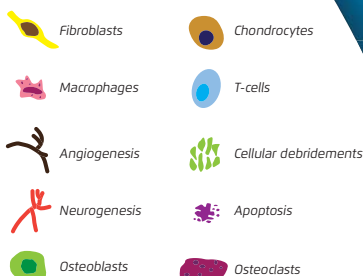
Osteophyte

4 PAIN

3 DEGENERATION

Chronic pain^{14,15,16} is the consequence, at least in part, of nociceptive stimulation of the joint capsule, synovial

LEGEND



INFLAMMATION AND OXIDATIVE DAMAGE

Flexide, an exclusive blend of natural extracts with **anti-inflammatory and antioxidant properties**, contains:

FLEXIDE



boswellia serrata

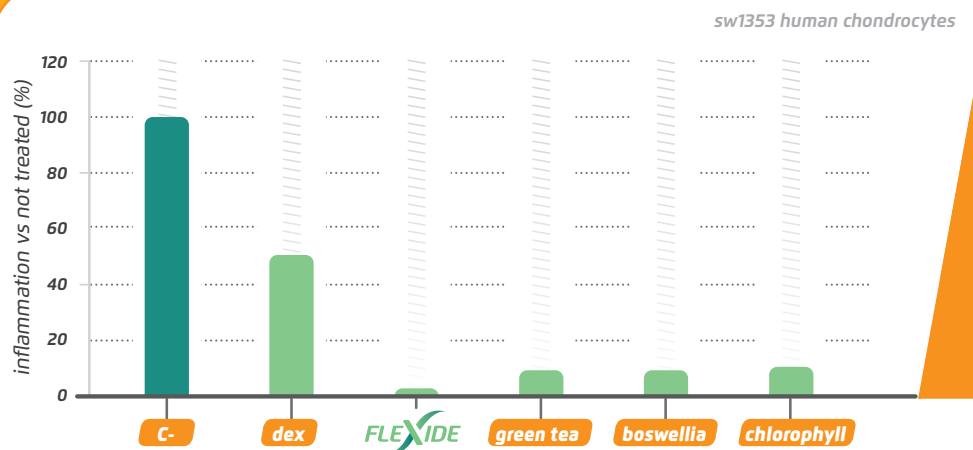


green tea

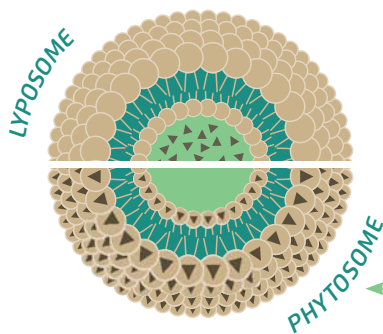


chlorophyll

In vitro assessment of Flexide blend's anti-inflammatory activity on human chondrocytes



Graph. 1 The trial was conducted using the sandwich ELISA method, following induction with $TNF-\alpha$, and detection of inflammatory cytokine IL-8. The activity was compared between C- induced cells, induced cells and cells with dexamethasone (Dex), with Flexide and with the separate extracts of the blend. Candioli, BICT. Data on file, 2018

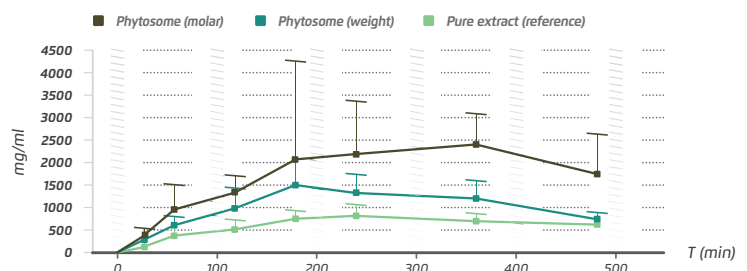


CASPEROME® BOSWELLIA

4 times more bioavailable^{9,13} thanks to the patented lecithin delivery technology **indena®**

▶ water-soluble active ingredient ● phosphatidylcholine ▲ phosphatidylcholine complex-active ingredient

membrane, ligaments and sub-chondral bone^{15,16,21}, activated by inflammatory cytokines (PG, LT) and free radicals (NO)^{7,21}



Graph. 2 Different plasma concentrations of β -boswellic acid following oral administration of Boswellia extract as such or Casperome®. Mod. da Hush et al, 2013

IMMUNE MODULATION

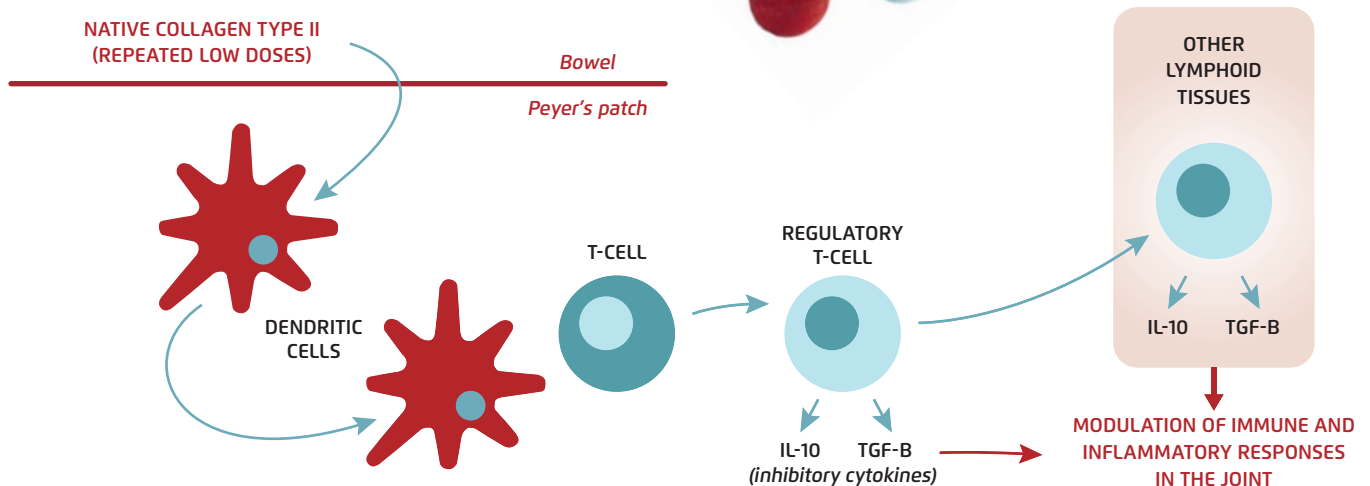


Collagen is a natural ingredient obtained from chicken sternum based on native collagen type II

- **Reduces collagen damage**^{6,17}
- **Reduces inflammation and joint pain**^{1,5,6}
- **Improves articular function**¹

Type II collagen is the main structural protein of cartilage, to which it provides strength and consistency^{2,7,19}.

Cartilage erosion and inflammation specific to OA are also consequences of a driven immune response against endogenous type II collagen^{11,17}



Native **type II collagen** modulates¹⁷, in small doses, the immune response by a mechanism called *Oral Tolerance* that consists of a decreased immune response to a previously administered antigen:

- penetration of Peyer's patches into the small intestine;
- interruption of the T-cell attack against endogenous type II collagen;
- induction of a reduced immune response
- reduction of inflammation and pain.

CARTILAGE METABOLISM

Chondroitin Sulfate

100% purity / molecular weight 16.9 kDa

EACH TABLET contains:

Chondroitin sulphate 300 mg

Glucosamine HCl

purity >99% / molecular weight 216 Da

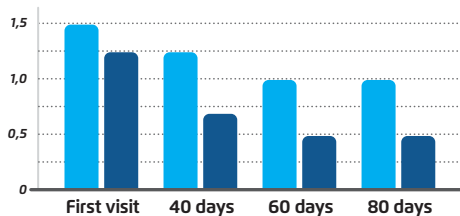
EACH TABLET contains:

Glucosamine (Chitosamine) (from animal tissues) 500 mg

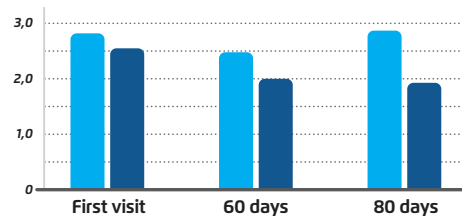
Effectiveness guaranteed by maximum level of purity and low molecular weight:

- In vitro protective and regenerative properties¹²
- In vivo efficacy in humans^{8,18} and dogs affected by OA^{20,24}

The assessment of the evolution of the global scores on the functional scale showed an improvement of 29.4% ($p < 0.05$) after 80 days (60 days of treatment and 20 days of follow-up) for the treated group and 0% in the placebo group³³ (Graph. 3-4).



Graph. 3 Development of the lameness degree during walking in animals suffering from hip osteoarthritis



Graph. 4 Evolution of the pain degree in animals affected by right hip osteoarthritis

Purity and molecular weight

THE BIOLOGICAL ACTIVITY OF CHONDROITIN SULFATE HAS AN INFLUENCE ON CARTILAGE¹²

Only CS with purity >99% showed anabolic and stimulating effects on the type II collagen synthesis, an essential constituent of the cartilage matrix, as well as on the reduction of PGE₂ synthesis.

Low-purity CS ($\leq 90\%$) can damage the joint instead of protecting it, accelerating cartilage degeneration and stimulating joint inflammation.

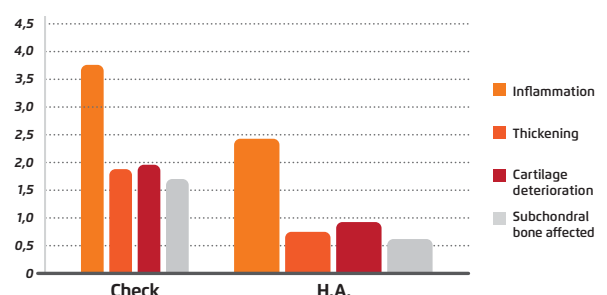
	ORIGIN	PURITY	EFFECTS ON CARTILAGE
CS1	Porcine	90.4%	↑ Production of catabolic factors (metalloproteases) ↓ Collagen synthesis
CS2	Bovine	96.2%	↓ Production of catabolic factors at 1000 mg/ml (dosages 5 times greater than CS3)
CS3	Bovine	99.9%	↓ Production of catabolic factors at 200 mg/ml (dosages 5 times lower than CS2) ↑ Collagen synthesis

Hyaluronic acid

NATURAL EXTRACT OF COCKSCOMB
HIGH (60%) HA CONTENT WITH LOW MOLECULAR WEIGHT ($1,2 \times 10^6$ kD)
PROVEN ORAL ABSORPTION (data on file Bioiberica)

ACTIVITY AT JOINT LEVEL → IN VIVO TRIAL⁴

Histopathological parameters of knees (inflammation, synovial thickening, cartilage deterioration, and subchondral involvement) in rats with experimentally-induced OA were **significantly lower** (51%, $p < 0.005$) in the group that took **hyaluronic acid** orally compared to the placebo control group.



Graph. 5 Histopathological parameters of the knee (inflammation, thickening, cartilage deterioration, subchondral bone affected) during hyaluronic acid administration

Confis ULTRA

Supports joint metabolism in case of osteoarthritis



COMPOSITION Glucosamine (Chitosamine) (from animal tissues), Salt of fatty acids from Linseed oil (Ω-3-linolenic acid), Chondroitin sulphate, Dicalcium phosphate, Pork by-products, Sugar, Yeast [Brewers' yeast], Vegetable by-products, Magnesium stearate, Hyaluronic acid, Fish oil, Collagen (extracted from chicken sternums).

ADDITIVES PER KG *Stabilizers:* Microcrystalline cellulose E460 mg 130,000 – Guar Gum E412 mg 40,000 *Sensory additives:* Camellia sinensis (L.) O. Kuntze: Tea extract CoE 451 mg 17,500 (*FleXide) - Boswellia serrata Roxb. ex Colebr.: Olibanum extract mg 15,750 (*FleXide) - Chlorophyll copper complex E 141 mg 1,750 (*FleXide) *Anticaking agents:* Colloidal silica E551b mg 9,000 *Vitamins:* Vitamin E 3a700 IU 6,250 *Preservatives, antioxidant*

ANALYTICAL CONSTITUENTS Crude protein 12.0% - Crude fibre 11.0% - Crude oils and fats 15.0% - Crude ashes 20.0% - Moisture content 5.0% – Total omega-3 fatty acids 3.4% -Total EPA 0.40% - Total Vitamin E 0.62%

EACH TABLET CONTAINS

Glucosamine (Chitosamine) (from animal tissues) (purity >99%)	500 mg	Hyaluronic acid	18 mg
Chondroitin sulphate (purity 100%)	300 mg	Collagen (extracted from chicken sternums)	4 mg

INSTRUCTION FOR PROPER USE

Confis ULTRA is a complementary feed for dogs, formulated to support joint metabolism in dogs suffering from osteoarthritis. Give **Confis ULTRA** directly into the mouth or mix with the regular serving according to the following daily amounts:

			Tablets per day			
0-5 kg			½ tablet		20-35 kg	3 tablets
5-10 kg			1 tablet		35-50 kg	4 tablets
10-20 kg			2 tablets		>50 kg	5 tablets

Recommended length of time: initially up to 3 months. It is recommended that a veterinary surgeon's opinion be sought before use or before extending the period of use. It is advisable to perform 2-3 cycles of 40 days of continuous administration to obtain the expected benefit on the joint metabolism. Tablets may be administered as a single daily dosage. *The minimum storage life means the period during which, under proper storage conditions the feed retains its properties. Keep the bottle closed after use. Keep in a dry place and protect from sunlight and heat sources before and after opening. Not for human consumption.*

Dietetic complementary feed for particular nutritional purposes for dogs

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