ClinicoEconomics and Outcomes Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Cost-Effectiveness of Chondroitin Sulphate (with or without Glucosamine) Prescription in the Treatment of Knee Osteoarthritis Compared to NSAIDs and COXIBs

Carlos Rubio-Terrés[1], Miguel Bernad Pineda[2], Josep Vergés[3]

[1]Health Economics Department, Health Value, Madrid, Spain; [2]Rheumatology Department, Hospital Universitario La Paz, Madrid, Spain; [3]CEO Department, Osteoarthritis Foundation International (OAFI), Barcelona, Spain

Correspondence: Carlos Rubio-Terrés, Health Economics Department, Health Value, C/ Virgen de Aránzazu, 21, Madrid, 28034, Spain, Email crubioterres@healthvalue.org

Background: Chondroitin sulfate, alone or associated with glucosamine (CS/CS+GLU), is an effective knee osteoarthritis (KOA) treatment, with fewer adverse effects (AEs) than non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 inhibitors (COXIBs).

Purpose: To estimate the CS/CS+GLU cost-effectiveness versus NSAIDs/COXIBs, due to the avoidance of mild-moderate or severe gastrointestinal AEs (GIAE), ischemic heart disease (IHD), acute kidney insufficiency (AKI), chronic kidney failure (CKF) and ischemic stroke (IS) from the Spanish National Health System (NHS) perspective.

Methods: Two analyses were considered: 1) savings to the NHS from current CS/CS+GLU treatment; and 2) maximum savings that could be achieved by the NHS if all patients with KOA currently treated with NSAIDs/COXIB would be switched to CS/CS+GLU. AEs frequency, associated utilities loss and managing cost were obtained from medical literature and Spanish sources. A probabilistic model (second-order Monte Carlo simulation) was carried out for a 3-year time horizon. Treatment duration: 180 days (base case); 90 and 240 days (sensitivity analysis).

Results: First analysis: 45,087 mild-moderate GIAE, 3,217 severe GIAE, 211 IHD, 1,087 AKI, 746 CKF and 3,359 IS, would be avoided with CS/CS+GLU. Discounting drugs cost, the three-year savings would be 57.1 million euros (savings probability: 80.7%). The savings per patient treated with CS/CS+GLU would amount to €38.02 (95% CI 14.06; €75.69), with a mean gain of 0.0023 (95% CI 0.0018–0.0027) QALY. The probability that CS/CS+GLU treatment was dominant (lower costs and QALY gain) or cost-effective (cost per QALY gained less than €25,000) was 80.7% and 98.1%, respectively. In the second analysis, savings for the NHS would amount to 387 million euros, with the CS/CS+GLU-only option being dominant and cost-effective in 100% of the analyses.

Conclusion: The improved tolerability of CS/CS+GLU versus NSAIDs/COXIBs is expected to prevent thousands of AEs and generate considerable savings for the NHS, making it cost-effective treatment.

Keywords: knee osteoarthritis, chondroitin sulfate, glucosamine, cost-effectiveness, budgetary impact, health impact

Introduction

Knee osteoarthritis (KOA) is the most common type of osteoarthritis (OA) in adults, characterized by a high rate of disability and poor quality of life.[1–3] Chondroitin sulfate alone (CS) (Condrosan®/Condrosulf®/Condroitin sulfato Kern Pharma®) or associated with glucosamine (CS+GLU) (Droglican®) (CS/CS+GLU) is one of the main constituent elements of cartilage, being indicated (alone or associated with glucosamine) in the symptomatic treatment of osteoarthritis.[4,5] Treatment of KOA with CS/CS+GLU has been associated with improvement in pain[6,7] and joint function.[8,9] Its efficacy has been confirmed in systematic reviews and meta-analyses[6,7,9–12] as well as in the

https://doi.org/10.2147/CEOR.S577731
Received: 30 October 2025
Accepted: 21 March 2026
Published: 6 May 2026

MOVES,[13] MOSAIC[14] and CONCEPT[15] clinical trials, in which CS/CS+GLU proved to be as effective as celecoxib after 6 months, but with a better safety profile.

On the other hand, as demonstrated in a meta-analysis,[16] CS/CS+GLU is well tolerated. In fact, CS/CS+GLU and glucosamine were not associated with an increased risk of adverse events (AE) compared to placebo.[16] This good tolerability of CS/CS+GLU contrasts with the toxicity problems described for NSAIDs/COXIBs[17] at gastrointestinal,[18] cardiovascular,[19,20] cerebrovascular[21] and renal[22] levels. The detrimental effects of continued NSAID use in osteoarthritis patients are well described in scientific literature. A 2019 study[23] involving more than 7,000 patients with osteoarthritis showed they had a 23% increased risk of developing cardiovascular disease compared to controls; and that a 41% increase in this risk was directly linked to NSAID use.

CS/CS+GLU is currently recommended for the treatment of KOA by, among others, the guidelines of the Spanish Society of Rheumatology (SER),[24,25] the European League Against Rheumatism (EULAR)[26] and those published by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).[27] Moreover, cardioprotective and cerebroprotective effect, based on reduced risk of acute myocardial infarction and ischemic stroke, revealed by Mazzucchelli et al, adjusts to the safety profile of OA patients, which usually have comorbidities that imply cardiovascular risk, similar as metabolic syndrome patients.[28]

In 2020, an economic analysis was published which concluded that, "due to its better tolerability profile, treatment with CS/CS+GLU is expected to prevent thousands of adverse events over the next three years in Spain, some of which may be life-threatening, while generating considerable savings for the Spanish National Health System. (NHS)"[29]. This study, however, was limited to the analysis of the costs and consequences of the better tolerability of CS/CS+GLU, but did not assess its cost-effectiveness compared to non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 inhibitors (COXIBs), ie the cost of quality-adjusted life years gained (QALYs) (calculated from the so-called "utilities", the quality of life perceived by the patient) and did not include the cardioprotective (reduced risk of acute myocardial infarction) and cerebroprotective (reduced risk of ischemic stroke) effects revealed in two nested case-control studies, published in 2021 and 2022, respectively.[20,21]

The aim of the present study was to estimate the cost-effectiveness of CS/CS+GLU compared with NSAIDs/COXIBs in the treatment of KOA, because of avoiding mild-moderate or severe gastrointestinal adverse events (GIAE), ischemic heart disease (IHD), acute kidney injury (AKI), chronic kidney failure (CKF) and ischemic stroke (IS) in Spain.

Methods

Economic Model

Based on the current situation (part of KOA patients treated with CS/CS+GLU and part treated with NSAIDs/COXIB), two analyses were performed: (i) To determine the savings to the NHS from current CS/CS+GLU treatments, it was hypothesized that all patients treated with CS/CS+GLU would be switched to NSAIDs/COXIBs. The additional costs that could result from this change would be the savings currently being generated by CS/CS+GLU treatments, due to their improved safety profile. (ii) To determine the maximum savings that could be achieved by the NHS, it was hypothesized that all patients with KOA currently treated with NSAIDs/COXIB would be switched to CS/CS+GLU.

In both analyses the following calculations were performed: a) estimation of the number of AE avoided with CS/CS +GLU in the Spanish population with KOA; b) estimation of the economic impact derived from the AE avoided with CS/CS+GLU in the Spanish population with KOA and probability of savings for the NHS for this concept; c) savings per patient with KOA associated with the utilization of CS/CS+GLU; d) QALYs gained per patient with KOA associated with the use of CS/CS+GLU; e) cost of gaining 1 QALY with CS/CS+GLU versus the hypothetical non-utilization of the treatment; f) probability that treatment with CS/CS+GLU is cost-effective (cost of gaining 1 QALY below €25,000) and/or dominant (with lower costs and gain in QALYs than without CS/CS+GLU).

A probabilistic model was performed using second-order Monte Carlo simulations,[30–32] with a hypothetical cohort of 1,000 iterations (patients, *lato sensu*), for a 3-year time horizon. This methodology allows the analysis of the uncertainty of the model variables.[32] The costs and utilities (continuous variables) were adjusted to gamma distributions; the probabilities of AE (dichotomous variables) were adjusted to beta distributions, in both cases according to the minimum

and maximum values described in the literature.[30,31] The annual variables of the model are summarized in Table 1 (probabilities) and Table 2 (costs and utilities). The number of adverse events avoided was obtained from the population treated with CS/CS+GLU or NSAID/COXIB. The probability of each adverse event with each treatment was calculated, using mean values and their 95% confidence intervals, through a second-order Monte Carlo simulation with 1,000 analyses.

Table 1 Annual Probabilities of Adverse Events with the Treatments Considered (Beta Distributions)

Adverse event	Items	CS/CS+GLU	NSAID/COXIB	References
Mild gastrointestinal	Mean ± SD Alpha Beta	0.0064 ± 0.0003 381 59,258	0.1386 ± 0.0071 331 2055	[18,29,33,34]
Severe gastrointestinal	Mean ± SD Alpha Beta	0.0000* – –	0.0090 ± 0.0005 380 41,918	[18,29,33,34]
Coronary ischemia	Mean ± SD Alpha Beta	0.00009 ± 0.00001 96 1,047,242	0.00069 ± 0.00004 384 552,286	[19]
Acute renal failure	Mean ± SD Alpha Beta	0.0000* – –	0.0031 ± 0.0002 383 123,766	[22]
Chronic renal failure	Mean ± SD Alpha Beta	0.0000* – –	0.0021 ± 0.0001 383 178,769	[22]
Ischemic stroke	Mean ± SD Alpha Beta	−0.0044 ± −0.0003** 194 44,945	0.0055 ± 0.0028 3.83 698	[21]

Notes: *No cases have been described in the available clinical studies. **This negative value does not, obviously, indicate a negative probability, but rather a reduction in the probability of ischemic stroke (IS) in patients treated with CS/CS+GLU.

Abbreviations: COXIB, cyclooxygenase 2 inhibitors; CS/CS+GLU, chondroitin sulphate with/without glucosamine; NSAID, non-steroidal anti-inflammatory drugs; SD: standard deviation.

Table 2 Costs and Utilities Considered in the Model (Gamma Distributions)

Item	Mean ± SD	Alpha	Beta	References
Annual treatment cost (180 days)*				[4,5,35–37]
CS (400 mg) (60 capsules)	67.08 €	–	–	
CS+GLU (1200+1500 mg) (90 capsules)	205.32 €	–	–	
NSAIDs/COXIBs	31.44 €	–	–	
Adverse events management unit cost				
Mild gastrointestinal	285.29 ± 14.56 €	384.16	0.74	[34,38]
Severe gastrointestinal	3,393.24 ± 1,023.24 €	10.99	308.56	[34,38]
Coronary ischemia	7,158.09 ± 730.42 €	96.04	74.53	[39]
Acute renal failure	7,203.53 ± 6,290.99 €	1.31	5494	[39]
Chronic renal failure	12,337.65 ± 7,848.16 €	2.47	4992	[39]
Ischemic stroke	9,285.45 ± 5,199.92 €	3.19	2912	[39]

(*Continued*)

Table 2 (Continued).

Item	Mean ± SD	Alpha	Beta	References
Utility in the patient with knee osteoarthritis	0.5320 ± 0.2870	3.4	0.1548	[40]
Utilities lost associated to adverse events**				
Mild gastrointestinal	−0.034	7607	0.0001	[41]
Severe gastrointestinal	–0.449	3852	0.0001	[41]
Coronary ischemia	-0.231	30,015	0.00002	[42]
Acute renal failure	–0.214	384	0.0018	[43]
Chronic renal failure	-0.334	36	0.0161	[43]
Ischemic stroke	–0.359	384	0.0015	[44,45]

Notes: *Public price without VAT; **Alpha and beta values of state utilities, not of state utility losses.
Abbreviations: COXIB, cyclooxygenase 2 inhibitors; CS, chondroitin sulphate; CS+GLU, CS with glucosamine; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

Population

The evolution of a hypothetical cohort of patients with KOA was modelled. The prevalence of KOA in Spain, in patients over 40 years of age, was obtained from the EPISER study of the Spanish Society of Rheumatology[46] (Table 3). The population over 40 years of age in Spain, projected for 2025–2027, was obtained from National Institute of Statistics

Table 3 Population Estimates for Spain Considered in the Study

Calculation of…	Item	Mean Value (Minimum-Maximum)	References
Prevalence of knee osteoarthritis (age ≥ 40 years)	-	13.9% (12.7–15.1%)	[46]
Population over 40 (± 1%)	2025	28,760,206 (28,472,604–29,047,808)	[47]
	2026	29,177,182 (28,885,410–29,468,954)	[47]
	2027	29,568,432 (29,272,747–29,864,116)	[47]
Estimated number of patients with knee osteoarthritis	2025	3,977,537 (3,604,632–4,389,124)	Calculation 1
	2026	4,035,204 (3,656,893–4,452,759)	Calculation 1
	2027	4,089,314 (3,705,930–4,512,468)	Calculation 1
% of patients with osteoarthritis receiving drug therapy	-	93.99% (91.02–94.11%)	[48,49]
% of patients with osteoarthritis treated with NSAIDs/COXIBs	Acc. to the MPR*	14.40%	[48]
% of patients with osteoarthritis treated with CS/CS+GLU	Acc. to the MPR*	21.2%	[48]
No. of patients with knee osteoarthritis treated with NSAIDs/COXIBs (MPR ≥ 50%) *	2025	538,342 (425,215–654,288)	Calculation 2
	2026	546,147 (431,380–663,774)	Calculation 2
	2027	553,471 (437,165–672,675)	Calculation 2
No. of CS+GLU units foreseen, based on annual sales up to January 2025 (± 10%) **	2025	539,144 (485,230–593,058)	Reig Jofre data on file, 2025
	2026	549,927 (494,934–604,920)	
	2027	560,925 (504,833–617,018)	
No. of units of CS, based on annual sales up to January 2025 (± 10%) **	2025	2,912,308 (2,621,077–3,203,539)	Reig Jofre data on file, 2025
	2026	2,970,554 (2,673,499–3,267,610)	
	2027	3,029,965 (2,726,969–3,332,962)	
Estimated number of patients treated with CS	2025	102,902 (92,611–113,192)	Calculation 3
	2026	104,960 (94,464–115,456)	Calculation 3
	2027	107,059 (96,353–117,765)	Calculation 3

(*Continued*)

Table 3 (Continued).

Calculation of…	Item	Mean Value (Minimum-Maximum)	References
Estimated number of patients treated with CS+GLU	2025	9,525 (8,572–10,477)	Calculation 4
	2026	9,715 (8,744–10,687)	Calculation 4
	2027	9,910 (8,919–10,901)	Calculation 4

Notes: Calculation 1: 28,760,206 ×13.9%=3,977,537 (the rest is the same). Calculation 2: 3,977,537 ×93.99%×14.4%=538,342 (the rest is the same). Calculation 3: For CS: (2,912,308 units×60 capsules per unit)/(2 capsules/day of CS [800 mg/day] ×180 days of treatment according to their summary of product characteristics) ×21.2% (MPR)= 102,902 patients[4] . Formula for estimating the patient sample size: Numerator: estimated number of capsules sold annually; Denominator: capsules consumed per patient, adjusted using the MPR. Calculation 4: For CS+GLU: (539,144 units×90 capsules per unit)/(6 capsules/day of CS+GLU [1200 mg/day] ×180 days of treatment) ×21.2% (MPR).[5] *MPR (*medication possession ratio)* ≥ 50% (regular use of the drug). **An annual increase in sales of 2% is expected.
Abbreviation: CS/CS+GLU: chondroitin sulfate with or without glucosamine.

database[47] (Table 3). The percentage of patients with KOA following pharmacological treatment was obtained from the EPISER study[46] (Table 3). The percentage of patients with symptomatic KOA treated regularly or occasionally with NSAIDs/COXIBs was obtained from two Spanish studies[48,49] (Table 3). "Regular" use was understood to mean a medication possession ratio (MPR) ≥ 50% and "occasional" use with an MPR ≥ 25% and <50%.[48]

Based on this data and the number of units sold in the year 2024 CS/CS+GLU (IQVIA market data, 2025), the number of patients with KOA treated with NSAIDs/COXIBs and CS/CS+GLU in Spain and in the Spanish regions was calculated (Table 3). Probabilistic analyses were performed based on the minimum and maximum values shown in Table 3. The details of the population calculations are presented in Table 3.

The two analyses were performed at the national level, with a sub-analysis also being conducted at the regional level.

Time Horizon

The simulation covered a period of 3 years (2025 to 2027). Probabilities, costs and utilities were calculated for annual cycles.

Perspective of the Analysis

The analysis perspective was that of the Spanish NHS, so only direct health costs were considered.

Costs Analyzed

The following costs were analyzed: (i) the cost of managing AE (mild-moderate or severe GIAE, IHD, AKI, CKF and IS); (ii) the drugs acquisition cost (CS/CS+GLU, NSAIDs/COXIBs). The costs are presented in euros (€) updated to 2024.

Probabilities and Costs of AE

The probabilities of the appearance of the different AEs are presented in Table 1. The unit costs of handling the AEs analyzed are shown in Table 2.

Gastrointestinal AE (GIAE)

The annual probabilities of suffering a mild-moderate GIAE (0.64% with CS/CS+GLU; 13.86% with NSAIDs/COXIBs) or severe (0% with CS/CS+GLU; 0.35% with NSAIDs/COXIBs) GIAE were obtained from the GI-REASONS study[18,33] (Table 1). These assumptions are more conservative than those adopted in the previously published VECTRA study.[34] The unit costs (updated to 2024) of a mild-moderate GIAE (€285) and a severe GIAE (€3,393) were obtained from the economic analysis published in 2020[29] (Table 2).

Ischemic Heart Disease (IHD)

The risk of suffering a myocardial infarction (MI) was obtained from the study by Mazzucchelli et al[20] In this nested case-control study, which included 23,585 incident MI cases and 117,405 controls (of which 89 cases and 757 controls received CS/CS+GLU), a cardioprotective effect was observed in patients treated with CS/CS+GLU, with an adjusted

odds ratio (AOR) of MI of 0.57 (95% CI 0.46–0.72). The probabilities of IHD considered in the model are presented in Table 1.

The economic impact of IHD was calculated from the public prices of DRG 121, 122, 123 and 140 (coronary ischemia, 7,158 €), according to the frequency observed in the study by the Jordi Gol Primary Care Research Institute[19,50] and health Spanish public prices[39] (Table 2).

Acute Kidney Insufficiency (AKI) and Chronic Kidney Failure (CKF)

The frequency of AKI (0.31%) and CKF (0.21%) associated with NSAIDs/COXIBs was obtained from the study by Nelson et al,[22] a retrospective study that included a large cohort of patients in the USA, treated with NSAIDs/COXIBs for at least 7 months of observation (Table 1). The economic impact of AKI and CKF was calculated from public health prices[39] (Table 2).

Ischemic Stroke (IS)

The risk of developing IS in patients treated with CS/CS+GLU or NSAIDs was obtained from two nested case-control studies.[21,51] The AOR of IS with CS/CS+GLU was 0.77 (95% CI 0.60–0.99)[21] and with NSAIDs it was 1.20 (95% CI 0.90–1.60).[51] Therefore, a possible protective effect of CS/CS+GLU on the risk of developing IS was observed (Table 1). The cost of IS (€9,285) was obtained from the public price of DRG 45[39] (Table 2).

The definitions of GIAE, IHD, AKI, CKF and IS were those described in the studies that provided the probabilities of such adverse events.[18,20–22,33,51]

Drugs Costs

The average annual cost of treatment with CS/CS+GLU is indicated in Table 2.[4,5,35–37] The average cost of CS/CS+GLU and NSAIDs/COXIBs was calculated for different durations of treatment over the period of one year: 180 days (6 and 12 packs for CS and CS+GLU treatment, respectively) in the base case of the analysis and 90 or 240 days (3 or 8 packs and 6 or 16 packs for CS and CS+GLU treatment, respectively) for the sensitivity analysis. According to its summary of product characteristics, CS/CS+GLU treatment should be carried out for at least 3 months, although in patients with significant inflammatory symptoms, after a rest period of 2 months, treatment could be started again following the same cycle.[4] Therefore, over the period of one year, CS/CS+GLU treatment could range from a minimum of 3 months to a maximum of 8 months. In the case of CS/CS+GLU with glucosamine, it is advisable to administer it for a period of at least 6 months.[5] With respect to NSAIDs/COXIBs, the duration of the treatment is highly variable, depending on the different studies. In the GI-REASONS study,[18,33] a randomized clinical trial aimed at analyzing the GIAEs associated with celecoxib and the NSAIDs/COXIBs, treatment duration was 6 months. This study was used to obtain the average frequency of GIAEs with NSAIDs/COXIBs used in the economic model. Consequently, an average treatment duration of 180 days, between a minimum of 30 and a maximum of 240 treatment days per year, was considered in the base case.

The average cost per patient treated with NSAIDs/COXIBs in the base case (180 days of treatment) was estimated at €31.44.[35–37] It was calculated from the report on the use of NSAIDs in Spain during the period 2013–2016, published by the Spanish Agency of Medicines and Medical Devices[35] and from prices by homogeneous grouping published by the Ministry of Health.[36] The daily doses of the various NSAIDs/COXIBs were obtained from the VECTRA study.[34]

Utilities

The utility value (the quality of life perceived by the patient, ranging from 1 -perfect health- to 0 -death-) of the patient with KOA (0.532) was obtained from the study by Martín et al[40] The utility loss associated with the different AEs was also obtained from the literature: −0.034 in mild GIAE and −0.449 in severe GIAE;[41] −0.231 in IHD;[42] −0.214 in AKI and −0.334 in CKF;[43] finally, −0.359 in IS[44,45] (Table 2).

Base Case and Sensitivity Analysis

In the two analyses carried out, a base case was considered for a treatment duration of 180 days. Sensitivity analyzes were performed for treatment durations of 90 and 240 days.

Results

National Results

First Analysis (Savings to the NHS from Current CS/CS+GLU Treatment)

In Spain, it is estimated that 538,342, 546,147 and 553,471 patients will be treated with NSAIDs/COXIBs with KOA and 112,426, 114,675 and 116,059 with CS/CS+GLU in 2025, 2026 and 2027, respectively (Table 3).

Due to better CS/CS+GLU tolerability, 45,087 mild-moderate GIAE, 3,217 severe GIAE, 211 IHD, 1,087 AKI, 746 CKF and 3,359 IS, would be avoided in 3 years (Table 4A). Therefore, it is estimated that for every 10,000 patients treated with CS/CS+GLU, 1,314 mild-moderate GIAE, 94 severe GIAE, 6 IHD, 32 AKI, 22 CKF and 98 IS, would be avoided. Discounting the cost of the drugs, the three-year net savings for the NHS would be 57.1 million euros, with a probability of savings with CS/CS+GLU of 80.7% (Table 4B). The savings per patient treated with CS/CS+GLU would amount to €38.02 (95% CI 14.06; €75.69), with a mean gain of 0.0023 (95% CI 0.0018–0.0027) QALY (Table 5). The probability that CS/CS+GLU treatment was dominant (lower costs and QALY gain) or cost-effective (cost per QALY gained less than €25,000) was 80.7% and 98.1%, respectively (Table 5). The result of the probabilistic analysis can also be seen in Figure 1.

Table 4 First Analysis (Population Level). Current Situation (Part of the Patients with KOA are Treated with CS/CS+GLU and Part are Treated with NSAIDs/COXIBs) Compared to a Hypothetical Situation in Which All Patients with KOA Currently Treated with CS/CS +GLU Would Be Treated with NSAIDs/COXIBS. A) Estimation of Adverse Effects Avoided and QALYs Gained with CS/CS+GLU (Treatment Duration: 180 Days). B) Economic Impact of KOA Treatment with CS/CS+GLU

A)

Year	Mild Gastrointestinal	Severe Gastrointestinal	Coronary Ischemia	Acute renal failure	Chronic Renal Failure	Ischemic Stroke	QALYs Gained in the Population
2025	15,065	1,041	69	354	243	1,107	1,473
2026	14,351	1,061	70	361	248	1,129	1,496
2027	15,671	1,116	72	372	255	1,158	1,518
Total	45,087	3,217	211	1,087	746	3,359	4,487

B)

Treatment Duration (Days)	Year	Annual Savings from Avoiding AE*	Annual Additional Cost of the CS/CS+GLU Treatment*	Annual Net Savings from Avoiding AE with the CS/CS +GLU Treatment*	Probability of Savings with CS/CS +GLU
180 [Base case]	2025	€24,438,169	€5,947,489	€18,490,680	80.7%
	2026	€25,286,906	€6,066,439	€19,220,467	
	2027	€25,631,842	€6,187,768	€19,444,074	
	Total	**€75,356,917**	**€18,201,696**	**€57,155,221**	
90	2025	€21,770,067	€2,971,242	€18,798,825	78.0%
	2026	€22,588,879	€3,030,667	€19,558,212	
	2027	€23,649,224	€3,091,280	€20,557,944	
	Total	**€68,008,170**	**€9,093,189**	**€58,914,981**	
240	2025	€26,757,748	€7,931,687	€18,826,061	83.0%
	2026	€27,659,775	€8,090,321	€19,569,454	
	2027	€27,337,324	€8,252,127	€19,085,197	
	Total	**€81,754,846**	**€24,274,136**	**€57,480,711**	

Notes: *The duration of treatment determines the frequency of occurrence of AEs. However, the annual frequency of AEs is low, so the duration of treatment and the estimated annual savings are not proportional for treatment periods of less than one year. The savings in the population due to the avoidance of AEs are lower the shorter the duration of treatment and vice versa. The longer the duration of treatment, the higher the additional cost of CS/CS+GLU. The net savings are greater the shorter the duration of treatment and vice versa. The numbers in bold indicate the total sum for the years 2025, 2026 and 2027.

Abbreviations: AE, adverse effects; COXIBs, cyclooxygenase 2 inhibitors; CS/CS+GLU, chondroitin sulphate with or without glucosamine (GLU); NSAIDs, non-steroidal anti-inflammatory drugs; QALY, quality-adjusted life-years.

https://doi.org/10.2147/CEOR.S577731

Table 5 First Analysis (Patient Level). Cost-Effectiveness of Current Situation (Part of the Patients with KOA are Treated with CS/CS +GLU and Part are Treated with NSAIDs/COXIBs) Compared to a Hypothetical Situation in Which All Patients with KOA Currently Treated with CS/CS+GLU Would Be Treated with NSAIDs/COXIBS. Treatment Duration: 180 Days

Comparators	Cost Per Patient Mean (95% CI)	QALYs Per Patient Mean (95% CI)	Cost Per QALY Gained with CS*	CS Dominance Probability*	CS Cost-Effectiveness Probability**
Current situation with CS/CS+GLU §	138.16 € (45.62; 318.97 €)	0.5224 (0.5205–0.5243)	The option with CS/CS+GLU vs without CS/CS+GLU is dominant	80.7%	98.1%
Hypothetical situation without CS/CS+GLU¶	176.19 € (59.68; 394.66 €)	0.5201 (0.5178–0.5225)			
Savings	38.02 € (14.06; 75.69 €)	0.0023 (0.0018–0.0027)			

Notes: §Part of patients are treated with CS/CS+GLU part are treated with NSAIDs/COXIBs. ¶Hypothetical situation: all patients currently treated with CS/CS+GLU would be treated with NSAIDs/COXIBs. * The option with CS/CS+GLU is dominant: it generates savings and QALY gains compared to the option without CS/CS+GLU. **The option with CS/CS+GLU is cost-effective (and dominant) compared to the option without CS/CS+GLU, with a probability of 98.1%, for a willingness to pay of €25,000.

Abbreviations: 95% CI, 95% confidence interval; COXIBs, cyclooxygenase 2 inhibitors; CS, chondroitin sulphate with or without glucosamine (GLU); NSAIDs, non-steroidal anti-inflammatory drugs; QALY, quality-adjusted life-years.

Considering a treatment duration of 90 days, the probability of cost-effectiveness and dominance with CS/CS+GLU was 96.8% and 78.0%, respectively. For a duration of 240 days, the values would be 98.0% and 83.0%, respectively. Considering the estimated minimum and maximum number of patients treated with CS/CS+GLU and NSAIDs/COXIBs, the result remained in the same line as the base case of the analysis.

Second Analysis (Maximum Savings That Could Be Achieved by the NHS if All Patients with KOA Currently Treated with NSAIDs/COXIB Were Switched to CS/CS+GLU)

In the purely hypothetical assumption that all KOA patients currently treated with NSAIDs/COXIBs were switched to CS/CS+GLU, a total of 306,460 mild-moderate GIAEs, 20,790 severe GIAEs, 1,392 IHD, 7,203 AKI, 4,967 CKF, and 22,838 IS episodes would be avoided. As a result of the avoided AEs, 30,366 QALYs would be gained in the KOA population, with a saving of more than 387 million euros (Table 6).

The savings per patient treated only with CS/CS+GLU would amount to €121.48 (95% CI 37.77; €280.69), with a mean gain of 0.0130 (95% CI 0.0140–0.0156) QALY (Table 7). The probability that CS/CS+GLU treatment was

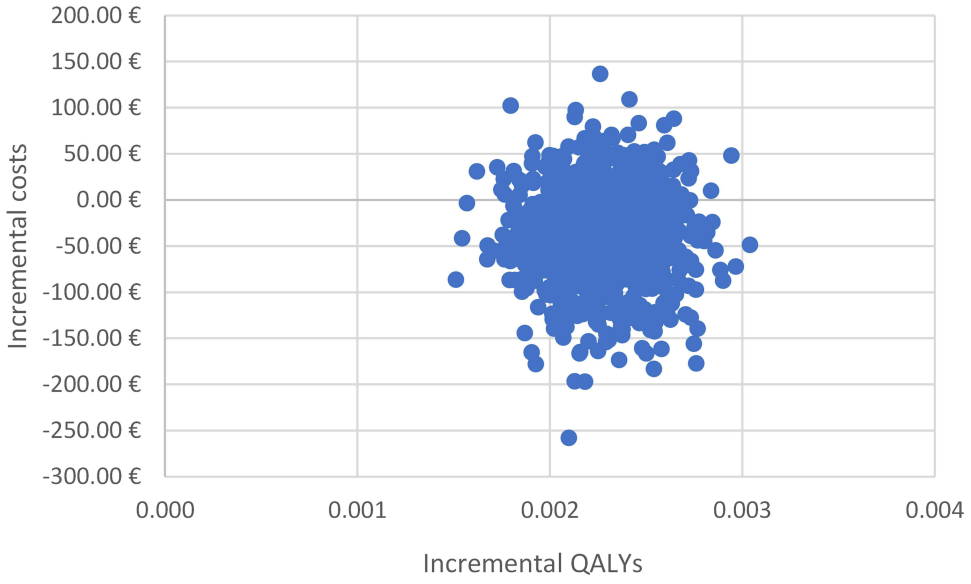

Figure 1 Cost-effectiveness of CS Prescription in the Treatment of Knee Osteoarthritis Compared to NSAIDs and COXIBs. Cost-effectiveness plane. Treatment duration: 180 days.

Abbreviations: COXIBs, cyclooxygenase 2 inhibitors; CS, chondroitin sulphate with or without glucosamine; NSAIDs, non-steroidal anti-inflammatory drugs; QALY, quality-adjusted life-years.

 https://doi.org/10.2147/CEOR.S577731

Table 6 Second Analysis (Population Level) (if All Patients with KOA Currently Treated with NSAIDS/COXIBS Were Treated with CS/CS+GLU Only). A) Estimation of Adverse Effects Avoided and QALYs Gained with CS/CS+GLU (Treatment Duration: 180 Days). B) Economic Impact of KOA Treatment with CS/CS+GLU

A)

Year	Mild Gastrointestinal	Severe Gastrointestinal	Coronary Ischemia	Acute Renal Failure	Chronic Renal Failure	Ischemic Stroke	QALYs Gained in the Population
2025	100,972	6,853	458	2,370	1,634	7,507	9,972
2026	101,497	6,958	465	2,406	1,659	7,622	10,124
2027	103,992	6,980	469	2,427	1,674	7,709	10,270
Total	306,460	20,790	1,392	7,203	4,967	22,838	30,366

B)

Treatment Duration (days)	Year	Annual savings from Avoiding AE*	Annual Additional Cost of the CS/CS+GLU*	Annual Net Savings from Avoiding AE with the CS/CS+GLU*	Probability of Savings with CS/CS +GLU
180 [Base case]	2025	€ 163,346,411	€ 36,322,477	€ 127,023,934	100%
	2026	€ 166,155,744	€ 36,878,377	€ 129,277,367	
	2027	€ 168,229,782	€ 37,408,709	€ 130,821,073	
	Total	**€ 497,731,937**	**€ 110,609,564**	**€ 387,122,373**	
90	2025	€ 164,259,220	€ 18,133,252	€ 146,125,968	100%
	2026	€ 167,086,658	€ 18,410,773	€ 148,675,885	
	2027	€ 170,499,598	€ 18,675,530	€ 151,824,067	
	Total	**€ 501,845,476**	**€ 55,219,555**	**€ 446,625,920**	
240	2025	€ 163,534,104	€ 48,450,697	€ 115,083,407	100%
	2026	€ 166,354,400	€ 49,192,214	€ 117,162,186	
	2027	€ 169,630,571	€ 49,899,626	€ 119,730,945	
	Total	**€ 499,519,075**	**€ 147,542,537**	**€ 351,976,538**	

Notes: *The duration of treatment determines the frequency of occurrence of AEs. However, the annual frequency of AEs is low, so the duration of treatment and the estimated annual savings are not proportional for treatment periods of less than one year. The savings in the population due to the avoidance of AEs are lower the shorter the duration of treatment and vice versa. The longer the duration of treatment, the higher the additional cost of CS/CS+GLU. The net savings are greater the shorter the duration of treatment and vice versa. The numbers in bold indicate the total sum for the years 2025, 2026 and 2027.

Abbreviations: AE, adverse effects; COXIBs, cyclooxygenase 2 inhibitors; CS/CS+GLU, chondroitin sulphate with or without glucosamine (GLU); NSAIDs, non-steroidal anti-inflammatory drugs; QALY, quality-adjusted life-years.

Table 7 Second Analysis (Patient Level) (if All Patients with KOA Currently Treated with NSAIDS/COXIBS Were Treated with CS/CS +GLU Only). Cost-Effectiveness of CS/CS+GLU in the KOA Treatment. Treatment Duration: 180 Days

Treatments	Cost Per Patient Mean (95% CI)	QALYs Per Patient Mean (95% CI)	Cost Per QALY Gained with CS/CS+GLU*	CS/CS+GLU Dominance Probability*	CS/CS+GLU Cost-Effectiveness Probability**
With CS/CS+GLU	51.98 € (20.16–116.29 €)	0.5332 (0.5329–0.5334)	The option with CS/CS+GLU vs without CS/CS+GLU is dominant	99.9%	100%
Without CS/CS+GLU	173.46 € (57.93–396.99 €)	0.5201 (0.5178–0.5225)			
Savings	121.48 € (37.77; 280.69 €)	0.0130 (0.0104–0.0156)			

Notes: *The option with CS/CS+GLU is dominant: it generates savings and QALY gains compared to the option without CS/CS+GLU. ** The option with CS/CS+GLU is cost-effective (and dominant) compared to the option without CS/CS+GLU, with a probability of 100%, for a willingness to pay of €25,000.

Abbreviations: 95% CI, 95% confidence interval; COXIBs, cyclooxygenase 2 inhibitors; CS/CS+GLU, chondroitin sulphate with or without glucosamine (GLU); NSAIDs, non-steroidal anti-inflammatory drugs; QALY, quality-adjusted life-years.

dominant (lower costs and QALY gain) or cost-effective (cost per QALY gained less than €25,000) was 99.9% and 100%, respectively (Table 7).

Regional Results

The regional results, in line with the national results, are presented in Tables S1 and S2 for analyses 1 and 2, respectively.

Discussion

Drug-induced AEs represent a significant cause of morbidity in developed healthcare systems with a relevant economic impact.[52,53] Therefore, an important aspect for determining the efficiency of a new therapy in KOA is to evaluate the AEs cost related to the symptomatic pharmacological treatment. This aspect has been previously evaluated in other indications, such as oncology and migraine.[54,55]

According to the present study, due to its improved tolerability profile, treatment with CS/CS+GLU would prevent thousands of AEs over the next three years. It is important to highlight the severity of some of these AEs, which can be life-threatening. This health impact would be accompanied by considerable savings for the NHS, making it cost-effective treatment.

To assess the reliability of these results, we must consider both the strengths and weaknesses of the study. The strength of the study is the consistency of the sources used to obtain the main variables for the analysis. Population data and AEs frequency data for the economic model were obtained, from epidemiological studies or databases[46,47,49] and from large-scale clinical trials[18,33] or observational studies.[20–22] The prevalence of KOA in Spain was obtained from the Spanish Society of Rheumatology, specifically from the EPISER study.[46] The population over 40 years of age in Spain was taken from the database of the National Institute of Statistics.[47] The percentage of patients with KOA who follow pharmacological treatment and the percentage of patients treated regularly or occasionally with NSAIDs/COXIBs were obtained from a study on the use of medicines in KOA in Spain,[48] which included 238,536 participants, followed between 2006 and 2010. Most of this data was used in a cost-consequences analysis published in 2020.[29]

While it is important to remember that this is a theoretical model (a simplified simulation of reality), a probabilistic model was developed to explore the effect of uncertainty in the model variables and to calculate the 95% confidence interval for the average results of the analysis (prevented AEs, total savings from prevented AEs, cost savings per patient, QALYs gained per patient, cost per QALY gained, probability of cost-effectiveness, probability of CS/CS+GLU dominance). The design of this type of model allows for a better simulation of clinical reality.[30–32] The suitability of the economic model was evaluated using the CHEERS checklist (Table S3).

The results obtained in this study are consistent with those obtained in three economic analyses previously published with data from Spain.[29,34,38]

Regarding weaknesses, the most notable is the calculation of the estimated number of patients treated with CS/CS +GLU or NSAID/COXIB, a calculation based on available epidemiological and population data and subjected to a sensitivity analysis. Furthermore, the study did not include patients receiving CS/CS+GLU and NSAIDs concomitantly, estimated at 12% of patients treated with CS/CS+GLU according to the VECTRA study[34] and 2.17% in the study by Wilson et al,[48] which should also be considered a limitation of the study. It should be noted that the average cost per patient for acquiring NSAID/COXIB was calculated based on data on the use of the different drugs in Spain.[35] The probability of adverse events was obtained from studies that analyzed NSAID/COXIB as a whole.[18,19,21,22,29,33,34] Another aspect to note regarding the second analysis is that the "maximum savings" scenario assumes that all KOA patients taking NSAIDs/COXIBs will switch to CS/CS+GLU. Obviously, it is a purely theoretical scenario. This may not be possible because of contraindications, differences in how patients respond, and doctor and patient preferences.

In this economic analysis, prescribing CS/CS+GLU for the treatment of KOA would be more efficient than prescribing NSAIDs and COXIBs. CS/CS+GLU is the dominant treatment (since it is more effective at a lower cost) compared to not prescribing CS/CS+GLU. However, the gain of 0.0023 QALYs per patient may not be clinically relevant.[56,57] If this premise were acceptable, up to €41 per patient treated with CS/CS+GLU would be saved compared to not receiving CS/CS+GLU treatment. This demonstrates that, in addition to the clinical value derived from using CS/CS+GLU, this alternative will generate resource savings for the NHS of Spain.

A fundamental difference between the present study and the one published in 2020 is due to the cost-effectiveness analysis carried out. It is important to note that the probability that the current use of CS/CS+GLU in KOA is "dominant" over a hypothetical situation without CS/CS+GLU use, with a probability of 80.7%. This means that in the 1,000 Monte Carlo simulations carried out, in 807 cases the treatment with CS/CS+GLU obtained more QALYs than without the utilization of CS/CS+GLU, also generating savings for the Spanish NHS. Furthermore, treatment with CS/CS+GLU was

"cost-effective" compared to the non-use of CS/CS+GLU, ie. the cost of gaining 1 QALY with CS/CS+GLU vs. without CS/CS+GLU was below 25,000 EUR (in Spain the cost-effectiveness threshold has been set between 25,000 and 60,000 EUR per QALY gained with the most effective drug).[58] The probability that CS/CS+GLU use is the cost-effective option would be 98.1% (it was cost-effective in 981 simulations out of 1,000 Monte Carlo iterations performed).

Conclusions

Due to its better tolerability profile, in the actual scenario CS/CS+GLU treatment is expected to prevent thousands of AEs over the next 3 years while generating considerable savings (57 million euros) for the NHS, being cost-effective treatment with a high probability. Considering the characteristics of osteoarthritis, other treatments should be considered (as the prescription of other pharmacological groups such as SYSADOAs to minimize the use of NSAIDs,[59] a hypothetical scenario where all the KOA patients actually treated with NSAIDs were treated with CS/CS+GLU is assessed: as a result of the avoided AEs, 30,366 QALYs would be gained in the Spanish population, with a potential saving for the NHS of more than 387 million euros.

Data Sharing Statement

Data accessed from the Spanish National Institute of Statistics database are freely available (www.ine.es). IQVIA market data: IQVIA is the data controller of the non-identifiable patient data used for the purposes of the study. Global sales data were managed in this study.

Ethics Statement

In any case were individual patient data handled; approval by an Ethics Committee was unnecessary, in accordance with Spanish legislation (Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry).

Funding

Study conducted with an unrestricted research grant from Reig Jofre.

Disclosure

The authors report no conflicts of interest in this work.

References

1. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5:e508–22. doi:10.1016/S2665-9913(23)00163-7
2. Veronese N, Honvo G, Bruyère O, et al. Knee osteoarthritis and adverse health outcomes: an umbrella review of meta-analyses of observational studies. *Aging Clin Exp Res*. 2023;35:245–252. doi:10.1007/s40520-022-02289-4
3. Vitaloni M, Botto-Van Bemden A, Sciortino Contreras RM, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. *BMC Musculoskelet Disord*. 2019;20:493. doi:10.1186/s12891-019-2895-3
4. Condrosan 400 mg hard capsules. CONDROSAN 400 mg granulate for oral solution. Summary of product characteristics. Available from: https://cima.aemps.es/cima/pdfs/es/ft/64549/64549_ft.pdf. Accessed February 20, 2025.
5. Droglican 200 mg/250 mg hard capsules. Summary of product characteristics. Available from: https://cima.aemps.es/cima/dochtml/ft/71394/FichaTecnica_71394.html. Accessed February 20, 2025.
6. Gregori D, Giacovelli G, Minto C, et al. Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA*. 2018;320:2564–2579. doi:10.1001/jama.2018.19319
7. Beaudart C, Lengelé L, Leclercq V, et al. Symptomatic efficacy of pharmacological treatments for knee osteoarthritis: a systematic review and a network meta-analysis with a 6-month time horizon. *Drugs*. 2020;80:1947–1959. doi:10.1007/s40265-020-01423-8
8. Honvo G, Bruyère O, Reginster JY. Update on the role of pharmaceutical-grade chondroitin sulfate in the symptomatic management of knee osteoarthritis. *Aging Clin Exp Res*. 2019;31:1163–1167. doi:10.1007/s40520-019-01253-z
9. Honvo G, Bruyère O, Geerinck A, Veronese N, Reginster JY. Efficacy of chondroitin sulfate in patients with knee osteoarthritis: a comprehensive meta-analysis exploring inconsistencies in randomized, placebo-controlled trials. *Adv Ther*. 2019;36:1085–1099. doi:10.1007/s12325-019-00921-w
10. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. *Curr Med Res Opin*. 2008;24:3029–3035. doi:10.1185/03007990802434932
11. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev*. 2015;1:. doi:10.1002/14651858.CD005614.pub2

12. Rabade A, Viswanatha GL, Nandakumar K, Kishore A. Evaluation of efficacy and safety of glucosamine sulfate, chondroitin sulfate, and their combination regimen in the management of knee osteoarthritis: a systematic review and meta-analysis. *Inflammopharmacology*. 2024;32:1759–1775. doi:10.1007/s10787-024-01460-9
13. Hochberg MC, Martel-Pelletier J, Monfort J, et al; MOVES Investigation Group. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis*. 2016;75:37–44.
14. Pelletier JP, Raynauld JP, Beaulieu AD, et al. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. *Arthritis Res Ther*. 2016;18:256.
15. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis*. 2017;76:1537–1543. doi:10.1136/annrheumdis-2016-210860
16. Honvo G, Reginster JY, Rabenda V, et al. Safety of symptomatic slow-acting drugs for osteoarthritis: outcomes of a systematic review and meta-analysis. *Drugs Aging*. 2019;36(Suppl 1):65–99. doi:10.1007/s40266-019-00662-z
17. Bernad M. Situación actual de los SYSADOA en España (Editorial). *Reumatol Clin*. 2016;12:181–183. doi:10.1016/j.reuma.2016.03.012
18. Cryer B, Li C, Simon LS, Singh G, Stillman MJ, Berger MF. GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial. *Am J Gastroenterol*. 2013;108:392–400. doi:10.1038/ajg.2012.467
19. Instituto de Investigación en Atención Primaria Jordi Gol. Riesgo cardiovascular en pacientes con osteoartritis: estudio de casos y controles Code: IJG-M01-2012-01. 2014;
20. Mazzucchelli R, Rodríguez-Martín S, García-Vadillo A, et al. Risk of acute myocardial infarction among new users of chondroitin sulfate: a nested case-control study. *PLoS One*. 2021;16:e0253932. doi:10.1371/journal.pone.0253932
21. Mazzucchelli R, Rodríguez-Martín S, Crespí-Villarías N, et al. Risk of ischaemic stroke among new users of glucosamine and chondroitin sulphate: a nested case-control study. *Ther Adv Musculoskelet Dis*. 2022;14:1759720X221113937. doi:10.1177/1759720X221113937
22. Nelson DA, Marks ES, Deuster PA, O'Connor FG, Kurina LM. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA Network Open*. 2019;2:e187896. doi:10.1001/jamanetworkopen.2018.7896
23. Atiquzzaman M, Karim ME, Kopec J, Wong H, Anis AH. Role of nonsteroidal antiinflammatory drugs in the association between osteoarthritis and cardiovascular diseases: a Longitudinal Study. *Arthritis Rheumatol*. 2019;71:1835–1843. doi:10.1002/art.41027
24. Blanco FJ. Panel of Experts of the Spanish Society of Rheumatology (SER). First consensus document of the Spanish Society of Rheumatology on the pharmacological treatment of knee osteoarthritis. *Reumatol Clin*. 2005;1:38–48. doi:10.1016/S1699-258X(05)72711-X
25. Benito-Ruiz P. Guías y recomendaciones para el diagnóstico y tratamiento de la artrosis: en busca del consenso. *Sem Fund Esp Reumatol*. 2012;13 (Suppl 1):1–32.
26. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidenced based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62:1145–1155. doi:10.1136/ard.2003.011742
27. Bruyere O, Reginster J-Y. Glucosamine and chondroitin sulfate as therapeutic agents for knee and hip osteoarthritis. *Drugs Aging*. 2007;24 (7):573–580. doi:10.2165/00002512-200724070-00005
28. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol*. 2012;8:729–737. doi:10.1038/nrrheum.2012.135
29. Rubio-Terrés C, Bernad Pineda M, Herrero M, Nieto C, Rubio-Rodríguez D. Analysis of the health and budgetary impact of chondroitin sulfate prescription in the treatment of knee osteoarthritis compared to NSAIDs and COXIBs. *Clinicoecon Outcomes Res*. 2020;12:505–514. doi:10.2147/CEOR.S265994
30. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford, UK: Oxford University Press; 2006.
31. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost–Effectiveness Analysis in Healthcare*. Oxford University Press; 2012.
32. Rubio-Terrés C, Rubio-Rodríguez D. Probabilistic analysis: sensitivity analysis or main result? (Editorial). *Pharmacoeconomics*. 2016;1:2.
33. GI-Reasons. A trial of GI safety of celecoxib compared with Non-Selective Nonsteroidal Antiinflammatory Drugs (NSAIDS) (GI-REASONS). Available from: https://clinicaltrials.gov/study/NCT00373685?tab=results. Accessed February 21, 2025.
34. Rubio-Terrés C, Grupo Del Estudio VECTRA. Evaluación económica del uso de condroitín sulfato y antiinflamatorios no esteroideos en el tratamiento de la artrosis. Datos del estudio VECTRA. *Reumatol Clin*. 2010;6:187–195. doi:10.1016/j.reuma.2009.12.009
35. AEMPS [Spanish Agency of Medcines and Medical Devices]. Consumo por principio activo en DHD. M01A. Productos antiinflamatorios y antir reumáticos no esteroideos (2023). Available from: https://app.powerbi.com/view?r=eyJrIjoiNzU2ODY3N2MtNGEyYS00N2MwLTg1ODgtOGM4YmNkNGJkYzAwIiwidCI6IjJkM2I1MGUwLTZlZjQtNGViYy05MjQ2LTdkMWNiYjc3MDg5YyIsImMiOjh9. Accessed March 25, 2026.
36. Agrupaciones homogéneas y solicitudes de bajadas voluntarias de precios - Febrero 2025. Información sobre agrupaciones homogéneas de medicamentos, sus precios menores y sus precios más bajos, actualizada a fecha 25 de febrero de 2025. Available from: https://www.sanidad.gob.es/areas/farmacia/infoIndustria/SPRAH/bajadasVoluntariasPrecios/2025/febrero.htm. Accessed March 25, 2026.
37. BotPlus. Available from: https://botplusweb.portalfarma.com/. Accessed January 21, 2025.
38. Rubio-Terrés C, Rubio-Rodríguez D, Möller I. Aproximación al impacto presupuestario y sanitario de la prescripción de condroitín sulfato en el tratamiento de la artrosis de rodilla y manos en comparación con los antiinflamatorios no esteroideos en Cataluña. *Pharmacoecon Span Res Artic*. 2017;14(1):19–25. doi:10.1007/s40277-016-0066-6
39. Orden 727/2017, dated 7 August, of the Regional Minister of Health, setting the public prices for the provision of health services and activities of the network of centres in the Community of Madrid. Official Gazette of the Community of Madrid No. 198. 2017.
40. Martín-Fernández J, García-Maroto R, Bilbao A, et al. Impact of lower limb osteoarthritis on health-related quality of life: a cross-sectional study to estimate the expressed loss of utility in the Spanish population. *PLoS One*. 2020;15:e0228398. doi:10.1371/journal.pone.0228398
41. Spiegel BM, Targownik L, Dulai GS, Gralnek IM. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Ann Intern Med*. 2003;138:795–806. doi:10.7326/0003-4819-138-10-200305200-00007
42. Morey JR, Jiang S, Klein S, et al. Estimating long-term health utility scores and expenditures for cardiovascular disease from the medical expenditure panel survey. *Circ Cardiovasc Qual Outcomes*. 2021;14:e006769. doi:10.1161/CIRCOUTCOMES.120.006769
43. Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. *PLoS Med*. 2012; 9:e1001307.

44. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011;31:800–804. doi:10.1177/0272989X11401031
45. Betegón L, Canal C, Escolar G, et al. Cost-effectiveness analysis of apixaban versus dabigatran for prevention of stroke in patients with non-valvular atrial fibrillation in Spain. *Eur J Clin Pharm*. 2014;16:325–338.
46. Blanco FJ, Silva-Díaz M, Quevedo Vila V, et al. en representación del Grupo de Trabajo del Proyecto EPISER2016. Prevalence of symptomatic osteoarthritis in Spain: EPISER2016 study. *Reumatol Clin*. 2020;S1699-258X(20):30023.
47. Población residente en España a 1 de enero, por sexo, edad y año. Resultados nacionales: serie 2018-2068. Población y fenómenos demográficos. Instituto Nacional de Estadística. Available from: https://www.ine.es/jaxi/Datos.htm?tpx=28858. Accessed January 03, 2025.
48. Wilson N, Sanchez-Riera L, Morros R, et al. Drug utilization in patients with OA: a population-based study. *Rheumatol*. 2015;54:860–867. doi:10.1093/rheumatology/keu403
49. Castro-Domínguez F, Vargas-Negrín F, Pérez C, Gutiérrez-Prieto H, Rebollo P. Unmet needs in the osteoarthritis chronic moderate to severe pain management in spain: a real word data study. *Rheumatol Ther*. 2021;8:1113–1127. doi:10.1007/s40744-021-00327-7
50. Catalan Institute of Health. Resolution SLT/353/2013 dated 13 February on the revision of public prices corresponding to the health services provided by the Catalan Institute of Health. *Official Gazette of the Government of Catalonia (Spain)*. 2013;6326.
51. Bak S, Andersen M, Tsiropoulos I, et al. Risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nested case-control study. *Stroke*. 2003;34:379–386. doi:10.1161/01.STR.0000053029.45352.A0
52. Ernst FR1, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc*. 2001;41:192–199.
53. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. *Am J Health Syst Pharm*. 2001;58:1126–1132. doi:10.1093/ajhp/58.12.1126
54. Isla D, De Castro J, Juan O, et al. Costs of adverse events associated with erlotinib or Afatinib in first-line treatment of advanced EGFR-positive non-small cell lung cancer. *Clinicoecon Outcomes Res*. 2016;9:31–38. doi:10.2147/CEOR.S121093
55. Irimia P, Santos-Lasaosa S, García Bujalance L, Ramos Pinazo L, Rubio-Rodríguez D, Rubio-Terrés C. Cost of fremanezumab, erenumab, galcanezumab and onabotulinumtoxinA associated adverse events, for migraine prophylaxis in Spain. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21:285–297. doi:10.1080/14737167.2020.1768850
56. Kaplan RM. The minimally clinically important difference in generic utility-based measures. *COPD*. 2005;2:91–97. doi:10.1081/COPD-200052090
57. Wee HL, Machin D, Loke WC, et al. Assessing differences in utility scores: a comparison of four widely used preference-based instruments. *Value Health*. 2007;10:256–265. doi:10.1111/j.1524-4733.2007.00174.x
58. Sacristán JA, Oliva J, Campillo-Artero C, et al. ¿Qué es una intervención sanitaria eficiente en España en 2020? *Gac Sanit*. 2019;34:189–193. doi:10.1016/j.gaceta.2019.06.007
59. Loza E. AINES en la práctica clínica: lo que hay que saber. *Inf Ter Sist Nac Salud*. 2011;35:88–95.