

Hyaluronic Acid in Regenerative Medicine: From Molecular Weight–Dependent Signalling and the Stem Cell Niche to Musculoskeletal and Aesthetic Practice — A Comprehensive Narrative Review

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Abstract

Background: Hyaluronic acid (HA) is the only non-sulfated glycosaminoglycan of the extracellular matrix and the molecule most often invoked to justify "regenerative" injectable therapy. The same polymer is marketed as joint lubricant, volumizer, dermal biostimulator and cell-delivery scaffold. This review reconciles that promise with clinical evidence, regulatory status, product heterogeneity and price reality.

Methods: Evidence was identified in a structured, non-systematic manner through PubMed/MEDLINE and the Cochrane Library, citation chaining from retrieved reviews and guidelines, official regulator and manufacturer sources (United States Food and Drug Administration [FDA] premarket-approval and clearance summaries, Federal Register, European Union guidance, Brazilian National Health Surveillance Agency [ANVISA], instructions for use), payer policies, public pricing files and focused web discovery, to 9 September 2026. Exact strings and yields were not preserved; no pooling, PRISMA-based screening, protocol registration, risk-of-bias scoring or de-novo certainty grading was undertaken, and certainty is reported as published by source syntheses. This is a narrative review, not a systematic review, umbrella review or meta-analysis.

Results: In knee osteoarthritis the largest meta-analysis (169 trials, 21,163 participants) found pain and function effects below the minimal clinically important difference, with heterogeneity above 75%, small-study effects and increased serious adverse events, at low certainty; smaller low-risk-of-bias and product-stratified syntheses report larger benefits, and guidelines diverge. Aesthetic HA reliably corrects volume for 6–24 months by product, against rare but poorly reversible vascular events and delayed inflammatory nodules. Regeneration claims for skin boosters rest on small, frequently industry-funded studies. Approved ophthalmic, adhesion-barrier and bulking applications work mechanically. Payment limits, wholesale and patient prices differ several-fold.

Conclusion: HA is a versatile regenerative platform and an effective volumiser, but evidence for true tissue regeneration remains weak. Product-level reporting, responder-based outcomes and separation of commercial from clinical claims are needed.

Keywords

Hyaluronic acid; Regenerative medicine; Viscosupplementation; Dermal fillers; Osteoarthritis; Extracellular matrix.

Introduction

Few molecules occupy as much conceptual territory in regenerative medicine as hyaluronic acid. Isolated from bovine vitreous humour by Meyer and Palmer in 1934, it is the only non-sulfated glycosaminoglycan, is not assembled on a protein core, and is polymerised at the plasma membrane and extruded directly into the extracellular space [1,2,4]. Its mass can exceed several million daltons, it binds water up to a thousand times its own weight, and its biological meaning depends on chain length rather than chemical modification [1,4,6].

That dependence of function on size is the intellectual foundation of the field. High-molecular-weight HA cross-links CD44 receptors as a "tissue integrity" signal dampening inflammatory cytokine production, whereas fragmented low-molecular-weight HA engages Toll-like receptors 2 and 4 as a danger signal driving interleukin-1 β , tumour necrosis factor- α and interleukin-6 [3]. A molecule that also sustains the mesenchymal stromal-cell niche [8] is a legitimate candidate scaffold for tissue engineering.

The marketplace, however, has moved faster than the evidence. The same polymer is sold as an intra-articular device restoring synovial viscoelasticity, a cross-linked gel projecting soft tissue, an intradermal "biostimulator" and a hydrogel carrier for cells — four claims resting on four different evidentiary standards and frequently conflated. Regulators have registered the same discomfort: in 2018 the FDA signalled its intent to reconsider whether intra-articular HA, regulated as a device acting by physical viscoelastic replacement, might act pharmacologically and belong in the drug framework [58,59].

This review therefore separates four categories of claim — biological plausibility and platform utility, symptomatic Viscosupplementation, volumisation and biostimulation, and demonstrated tissue regeneration; presents the conflicting osteoarthritis evidence and discordant guidelines with their methodological causes; and supplies the product literacy the literature usually omits. Brand-level tables serve that purpose alone and constitute neither endorsement nor comparative clinical-effectiveness evidence.

Materials and Methods

Design and rationale

This is a comprehensive narrative review with structured evidence identification and explicit, source-

attributed evidence certainty, submitted as a Review Article. It is deliberately not presented as a systematic review, umbrella review or meta-analysis. The clinical questions are not commensurable: knee osteoarthritis (169 randomised trials) [9], hip and glenohumeral osteoarthritis [25,28], premarket-approval-based filler evidence [56] and chronic wound care (12 trials of very low certainty) [48] cannot be pooled into an interpretable estimate. An umbrella design would be structurally empty across half the scope, because the aesthetic vascular-occlusion literature is expert consensus at Level of Evidence 5 [35] and the review underpinning dermatologic-surgery guidance is of very low certainty [39]; and guideline discordance is itself an object of analysis that pooling cannot address [19,20,22,24].

Evidence identification

Sources were identified through PubMed/MEDLINE and the Cochrane Library, citation chaining from retrieved systematic reviews, meta-analyses and guidelines, official regulator sources (FDA device, premarket-approval and panel documents; the Federal Register; EUR-Lex and Medical Device Coordination Group guidance; ANVISA communications), manufacturer instructions for use, payer policies, the Medicare Part B average sales price file and focused web discovery for commercial and price information. The same approach was extended to the open FDA premarket-approval, clearance and recall databases, FDA summaries of safety and effectiveness data, European Union summaries of safety and clinical performance, the Medicare payment-limit files effective 1 July and 1 October 2026, the September 2026 National Health Service (NHS) Drug Tariff Part IX and European Central Bank reference exchange rates, giving a cut-off of 9 September 2026 [138,139,154–156,158]. Search concepts combined substance terms (hyaluronic acid, hyaluronan, sodium hyaluronate, hylan, NASHA, viscosupplementation) with indication, mechanistic and study-design descriptors. Per-source extraction records were kept, but exact database-by-database strings and numerical yields were not preserved, so the process is reported as structured and transparent rather than systematic or reproducible.

Once retrieved, sources were prioritized in this order: systematic reviews and meta-analyses; large randomised trials and long-term extensions; guidelines and consensus statements; regulatory documents; seminal mechanistic reports; and post-marketing surveillance analyses. Regulatory, labelling, payer, surveillance and pricing material was used only for regulatory, product-specification, safety-signal and price facts, never as evidence of efficacy. Device-report counts are reported as published in the FDA dermal-filler panel executive summary, not from any database query performed for this review [56].

What was not done

Screening and source selection were performed by the single author without independent duplicate screening; no numerical record of yields, duplicate removal or stage-by-stage exclusions was kept, so no study-selection flow diagram is presented and no compliance with PRISMA 2020 is claimed. No protocol was registered, including with PROSPERO. No risk-of-bias instrument was applied and no de-novo GRADE assessment was performed: every certainty statement is reported as published by its source, and where a source reported none, this is stated as "not reported". No quantitative pooling was undertaken. Consequences for interpretation are set out in Section 5.

Interpretive framework

Clinical claims were assigned to four tiers used throughout: Tier 1, biological plausibility and platform

utility, informative about potential but not clinical benefit; Tier 2, symptomatic viscosupplementation, meaning randomised evidence of pain or function change judged against a stated minimal clinically important difference and an adequate comparator; Tier 3, volumisation and biostimulation, separating premarket-approval-grade evidence of soft-tissue correction from claims about dermal quality or neocollagenesis; and Tier 4, demonstrated tissue regeneration, meaning durable, controlled restoration of tissue architecture and function. Indications are also labelled approved routine use, off-label, investigational or marketing claim. Prices are labelled by type — [ASP] Medicare average sales price payment limit, [ASP-calc] a course cost calculated for this review from the payment limit and labelled regimen, [DIST] distributor or wholesale list price, [CASH] consumer retail or discount-card price, [PATIENT] patient-facing or direct-pay price — all in United States dollars (USD) with access or effective dates, never mixed within a comparison. Prices originally quoted in euro or pound sterling were converted at European Central Bank reference rates for 8 September 2026, with the original currency retained [158]. Tables 1–14 appear consecutively in the Tables section.

Results

Endogenous biology and molecular-weight–dependent signalling

HA is a linear polymer of alternating (1→4)-β-D-glucuronic acid and (1→3)-β-N-acetyl-D-glucosamine, identical in vertebrates and bacteria — which makes bacterial fermentation a chemically faithful alternative to avian extraction [1,2,4]. HAS2 dominates adult tissue and is the only synthase whose deletion is lethal; catabolism proceeds through hyaluronidases and oxidative depolymerisation [1,3,4]. A 70-kg adult carries about 15 g and turns over 5 g daily, with residence times from minutes in plasma to 24 hours in skin and one to three weeks in cartilage [1,2,4].

One pharmacokinetic fact frames the debate: unmodified HA injected into a joint dissipates within 14–18 hours, whereas stabilised non-animal HA (NASHA) has a terminal half-life of about four weeks in the human knee [2,17]. No formulation persists across the three to six months over which benefit is claimed — the observation the FDA used when questioning the purely mechanical rationale for device classification [58].

Size thresholds are defined inconsistently across disciplines, and the inconsistency propagates into marketing: immunology treats above 5×10^5 Da as high molecular weight, polymer science sets the boundary at 10^6 Da, and in one binding study only chains above 700 kDa bound CD44 reliably [3,4]. Native articular HA measures 4×10^6 to 10^7 Da, so essentially every marketed viscosupplement is smaller than the molecule it replaces [2]. High-molecular-weight HA is additionally anti-angiogenic and enhances regulatory T-cell viability, whereas low-molecular-weight HA drives nuclear factor-κB translocation and angiogenesis [3,4]. Two corollaries follow: inflammation is self-reinforcing at matrix level, because fragmentation lowers synovial-fluid viscosity while generating pro-inflammatory fragments implicated in cartilage degeneration and pain [4]; and the anti-inflammatory reading of exogenous HA is defensible only for genuinely high-molecular-weight preparations [3,6].

HA as a regenerative platform

Tier-1 evidence is strong. Bone-marrow-derived mesenchymal stromal cells synthesise large quantities of HA and retain CD44-dependent pericellular coats associated with stemness, and HA structures form the

provisional matrix of early wound repair [3,8]. The same biology carries a caution: excess HA production promotes cancer-stem-cell signatures, and CD44 overexpression is associated with poor prognosis in several carcinomas [4,5,8]. As a biomaterial, HA cannot gel unaided: cross-linking, dominantly with 1,4-butanediol diglycidyl ether (BDDE), is required, and HA is a leading bioink candidate [5,7].

Translation to Tier-4 claims is where the field stalls. A phase I/II trial of allogeneic umbilical cord blood-derived mesenchymal stromal cells in an HA hydrogel treated seven patients with grade 3 osteoarthritis: pain and function improved at 24 weeks (both $p = 0.018$), with hyaline-like cartilage at one year — yet the authors attributed the effect to paracrine stimulation of endogenous chondroprogenitors, transplanted cells having disappeared by four to eight weeks in animal models [54]. Conversely, the pivotal FastTRACK phase III trial of an HA-based resorbable scaffold with bone-marrow aspirate concentrate versus microfracture met neither co-primary endpoint (pain $p = 0.81$; function $p = 0.34$), although responder analyses favoured the scaffold (≥ 15 -point pain improvement 83.5% versus 60.8%, $p = 0.004$) [55]. Convincing histology without a control arm and a failed randomised co-primary endpoint are not contradictory but the expected consequence of design, and post-hoc rescue analyses must be labelled as such.

Musculoskeletal evidence

Product class and regimen

Viscosupplements differ along five axes — origin, average molecular weight (500–730 kDa to more than 100,000 kDa), architecture, concentration and dose per course (8–22 mg/mL; 16.8–88 mg) and regimen (one to five injections) [17,18,29]. (**Table 1**) summarises class-level advantages and disadvantages; (Tables 8 and 9) give product-level detail for 34 products, nine of them marketed outside the United States and added here: the ARTHRUM family, including a chondroitin-sulfate variant, with strict OMERACT-OARSI response of 68.4%–91.2% in its own pooled analysis [110,141]; Adant, the formulation behind the US GenVisc 850 device, whose AMELIA trial sustained superiority over placebo to 40 months [18,142]; the avian Artz platform underlying Supartz [18,107]; Hyalubrix and Hyalubrix 60 for hip disease [123]; one European platform sold at three concentrations and as a hybrid, whose 0.8% version is the approved US Gelsyn-3 device [109,143,144]; and a cross-linked single injection non-inferior to stabilised HA in a randomised European trial [111]. Class effects are supported directionally: across 68 studies, products averaging $\geq 3,000$ kDa showed more favourable efficacy and fewer discontinuations than products at or below 1,500 kDa, and bio-fermentation HA produced less effusion and fewer flare-ups than avian HA, although effect sizes and certainty were unavailable [12]. The origin signal is quantified elsewhere as acute flare-up rates of 3.04% for bio-fermentation versus 13.19% for avian HA ($p < 0.05$) [32], and in one network meta-analysis high-molecular-weight HA was the only intra-articular treatment consistently exceeding the minimal clinically important difference at three months [16]. Regimen intensity is unsupported: across 11 studies there was no consistent difference between single- and multiple-injection formulations and no superiority of five- over three-injection courses [13].

Class (defining features)	Favourable characteristics	Unfavorable characteristics	Sources
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Low/medium-molecular-weight linear intra-articular HA (≈ 500 – $1,200$ kDa; 3–5 weekly injections)	Longest regulatory and clinical track record; lowest per-dose Medicare payment limit in the class; well-characterised formulations; bio-fermentation versions available	Less favourable efficacy than products $\geq 3,000$ kDa; more discontinuations for treatment-related adverse events than $\geq 3,000$ kDa; did not consistently exceed the minimal clinically important difference in network analysis; multiple clinic visits	[12,16,66]
High-molecular-weight linear intra-articular HA ($\approx 1,000$ – $3,600$ kDa; 3–4 injections)	Falls within or near the more favourable $\geq 3,000$ kDa efficacy band; bacterial-fermentation origin with less effusion and fewer acute flare-ups than avian HA	Still requires multiple visits; labelled molecular-weight ranges straddle the $3,000$ kDa threshold, so class assignment is imprecise	[12,18]
Cross-linked avian hylan (hylan G-F 20, $6,000$ kDa; 3 injections or single 6 mL dose)	Most extensively studied single product family; single-injection option delivering the full 48 mg dose	Avian origin, with pooled acute flare-up rate 13.19% versus 3.04% for bio-fermentation HA; implicated in 89.3% of published pseudoseptic-arthritis knees; inferior to stabilised ultra-high-molecular-weight HA at six months in one 182 -knee comparison	[12,17,32]
Stabilised ultra-high-molecular-weight gel (NASHA, $>100,000$ kDa, $\sim 1\%$ cross-links; single 3 mL/ 60 mg injection)	Single injection; approximately 4-week intra-articular half-life versus under 1 day for unmodified HA; non-inferior to methylprednisolone with superiority at week 26; matched allogeneic mesenchymal stromal cells at 12 months	Highest local adverse-effect rate among molecular-weight classes in hip osteoarthritis (37.5% , including 2 of 40 severe); inferior to hylan G-F 20 on WOMAC in one 227 -patient comparison	[13,17,27]
Fully cross-linked photo-gelation hydrogel (single 3 mL/ 30 mg injection)	Single low-volume injection of a 100% cross-linked hydrogel	Avian source; no formulation molecular weight reportable; second-highest per-dose payment limit in the class	[18,66,75]
Non-cross-linked chemically modified derivative (hexadecylamide HYADD4, 500 – 730 kDa; 2 injections)	Only two injections per course; bacterial-fermentation origin; chemically modified hydrogel without covalent cross-linking	Low molecular weight; highest calculated Medicare course cost in the class; no generic alternative	[18,66]
Aesthetic low- G' , low-swelling intradermal gels ("skin boosters", 12 – 20 mg/mL)	Target dermal hydration, texture and elasticity; lightly cross-linked formulations reduce papule risk; one product carries a label-defined protocol and annual volume cap	No volumising effect; evidence base largely observational and heterogeneous; several marketed products are not listed among FDA-approved fillers	[42,44,45,74]
Aesthetic high- G' cross-linked volumising gels ($G' \approx 400$ – $1,055$ Pa)	Predictable projection and durability up to 24 months at some sites; fully reversible with hyaluronidase	Deployed in high-risk anatomical zones; suprapariosteal placement is the setting of the bone-resorption signal; low-molecular-weight-containing families report the highest late-onset reaction rates	[34,36,56,67]
Non-cross-linked hybrid cooperative complexes (32 mg/mL, high- plus low-molecular-weight HA)	Largest post-marketing exposure dataset of any product reviewed, with a low reported adverse-event rate	Efficacy base of 9 small, mostly single-centre, manufacturer-funded studies; not listed among FDA-approved fillers; exposure denominator is modelled, not measured	[46,47]

Table 1: Favourable and unfavourable characteristics of the principal hyaluronic acid classes.

Knee osteoarthritis: the same question, five answers

(Table 2) sets the principal syntheses side by side; their divergence is the core of this review. The largest, 169 randomised trials and 21,163 participants, found pain standardised mean difference (SMD) -0.08 (95% CI -0.15 to -0.02) and function SMD -0.11 versus placebo — far below the stated minimal clinically important difference of SMD 0.37 — with heterogeneity of 75%–78%, increased serious adverse events, positive Egger's tests and low GRADE certainty throughout [9]. An earlier analysis of 89 trials in 12,667 adults reported an overall pain effect of -0.37 that fell to -0.11 in 18 large blinded trials — called clinically irrelevant by its authors — and to -0.03 among five unpublished trials [10]. Conversely, a synthesis of eight low-risk-of-bias trials with saline comparators found pain SMD -0.21 (95% CI -0.32 to -0.10) with heterogeneity of 32% and no evidence of publication bias, reading 0.21 as clinically relevant at the individual-patient level [11]. Product-level data add resolution that pooled estimates cannot: across 11 studies of NASHA at 3 mL/60 mg, a single injection was superior to hylan G-F 20 at six months ($p < 0.001$), non-inferior to methylprednisolone acetate, superior to saline in knees without effusion (40.6% versus 19.7%) and clearly inferior to plasma rich in growth factors [17].

Synthesis	Trials / participants	Pain effect	Function effect	Safety	Heterogeneity and bias	Certainty as reported	Source
Largest meta-analysis versus placebo	169 / 21,163	SMD -0.08 (95% CI -0.15 to -0.02) versus MCID 0.37	SMD -0.11 (-0.18 to -0.04)	Serious adverse events RR 1.49 (1.12–1.98); local RR 1.69 (1.12–2.56); gastrointestinal RR 1.07 (0.94–1.21)	I^2 75% (pain), 78% (function); funnel asymmetry; Egger's test positive	Low (GRADE) for all five outcomes	[9]
Guideline-anchoring meta-analysis	89 / 12,667	Overall -0.37 (-0.46 to -0.28); large blinded trials -0.11 (-0.18 to -0.04); unpublished trials -0.03 (-0.14 to 0.09)	Not tabulated here	Serious adverse events RR 1.41 (1.02–1.97); flare-ups RR 1.51 (0.84–2.72)	Important between-trial heterogeneity; asymmetrical funnel plot; effect associated with trial size, blinding and publication status	Not reported	[10]
Low-risk-of-bias subset	8 / 2,199	SMD -0.21 (-0.32 to -0.10)	SMD -0.12 (-0.22 to -0.02)	Not tabulated here	I^2 32% (pain), 0% (function); no funnel or Egger evidence of bias	Not reported	[11]
Product-differences meta-analysis	68 studies	Directional: $\geq 3,000$ kDa more favourable than $< 3,000$ kDa	Not reported	Fewer discontinuations for $\geq 3,000$ kDa than $\leq 1,500$ kDa; less effusion and fewer flare-ups with bio-fermentation HA	Effect sizes, confidence intervals and I^2 not available	Not reported	[12]

Guideline-commissioned analysis	AAOS systematic review	Effect less than 0.5 minimal-important-difference units; number needed to treat 17	Effect most evident at 6 weeks and 3 months	Not tabulated here	Downgraded one level for lack of generalised results	Moderate strength (downgraded)	[22,23]
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Table 2: Pivotal syntheses of intra-articular hyaluronic acid in knee osteoarthritis.

SMD, standardised mean difference; MCID, minimal clinically important difference; RR, relative risk.

Platelet-rich plasma, combinations and other joints

Comparative evidence favours platelet-rich plasma over HA while remaining fragile: a fragility-index meta-analysis of 1,993 patients found successful outcomes at odds ratio 2.19 (95% CI 1.33–3.62), yet a mean of only 8.67 outcome events per meta-analysis was needed to reverse significance [15]. A guideline work-group analysis found an advantage for platelet-rich plasma on total WOMAC at nine to twelve months [22], and a network meta-analysis of 35 studies ranked it and the HA–platelet-rich plasma combination above HA alone without publishing effect estimates or certainty ratings [14]. Platelet-rich plasma is thus the most consistently favourable adjunct, while combinations with fibrinogen, botulinum toxin A, stem cells and peptides remain investigational [16]. Outside the knee (**Table 3**) the evidence is thinner: all hip arms improve, between-group differences are absent at three to four months and a molecular-weight advantage appears later on pain but not function [25], a four-study meta-analysis found no significant effect [26], and local adverse effects rose with molecular weight to 37.5% for ultra-high-molecular-weight product [27]; shoulder data are favourable but methodologically weak [28], ankle data cover safety only [29], and the trapeziometacarpal joint has one uncontrolled series with 48% attrition at 12 months [30]. Beyond the joint cavity, three labelled preparations — peritendinous, post-arthroscopic and small-joint — rest on summaries of product characteristics rather than trials (**Tables 8 and 9**) [145–147].

Joint	Evidence base	Principal findings	Safety	Source
Hip	Level I systematic review, 7 randomised trials, 982 patients	All arms improved from baseline; no between-group difference at 3–4 months; at 4–6 months high-molecular-weight HA lower pain than medium-molecular-weight (MD –1.4; 95% CI –2.1 to –0.7), placebo (–1.6; –2.1 to –1.1) and control (–1.3; –1.8 to –0.8); WOMAC high versus medium $p = 1.0$	Not tabulated	[25]
Hip	Meta-analysis of high-molecular-weight HA, 4 studies	Pain SMD –0.056 (–0.351 to 0.239; $p = 0.709$); Lequesne function SMD –0.114 (–0.524 to 0.296; $p = 0.585$)	Complications RR 0.879 (0.527–1.466; $p = 0.622$)	[26]
Hip	Molecular-weight stratified review, 15 studies, 614 patients, 633 hips	Not pooled for efficacy	Local adverse effects 9.5% low, 8.2% medium, 12.2% high, 37.5% ultra-high molecular weight; systemic effects 0–0.6%	[27]
Shoulder (glenohumeral)	15 randomised studies, 1,023 subjects	HA plus physical therapy superior to physical therapy alone (overall effect size 4.43; $p = 0.00006$); HA superior to corticosteroid on pooled pain ($p = 0.002$)	Adverse-event rates not reported; no complications in 88 patients in a separate assessment	[28,29]

Ankle	Health-technology assessment, 76 patients across two studies	Pooled efficacy estimates not available	No severe treatment-related adverse events (0/21 and 0/55)	[29]
Trapeziometacarpal	Uncontrolled pilot study, 29 patients, 500–730 kDa, five weekly ultrasound-guided injections	Resting pain 5.31 ± 1.87 to 1.07 ± 1.71 at 1 month and 1.00 ± 2.24 at 12 months ($p < 0.001$); no further gain after month 1	No severe events; transient injection-site pain most frequent	[30]

Table 3: Hyaluronic acid in joints other than the knee.

MD, mean difference; SMD, standardised mean difference; RR, relative risk.

Guidelines and why they disagree

(Table 4) presents the positions. The 2019 American College of Rheumatology/Arthritis Foundation guideline conditionally recommends against intra-articular HA in the knee and first carpometacarpal joint and strongly against it in the hip, preferring glucocorticoid and recommending strongly against platelet-rich plasma [20]. The American Academy of Orthopaedic Surgeons 2021 guideline states that HA "is not recommended for routine use" at Moderate strength after a one-level downgrade, quantifying the effect below 0.5 minimal-important-difference units with a number needed to treat of 17 [21,22] — wording softened during peer review and clarified as pertaining to first-line treatment [23] — while the 2019 Osteoarthritis Research Society International guideline rates it Level 1B/Level 2 for the knee depending on comorbidity and does not recommend it for hip or polyarticular disease [19]. The counter-position must be represented: of 22 organisations identified in a rheumatology commentary, 19 (86%) were neutral or in favour for knee pain, and a separate review found 81% of guidelines favourable or neutral [24]. The guideline authors' own reasoning is explicit — benefit was restricted to higher-risk-of-bias studies — and their recommendation is stated not to be intended to influence insurance coverage [20].

Guideline	Knee	Hip	Hand	Related positions	Source
American College of Rheumatology / Arthritis Foundation 2019	Conditionally recommended against	Strongly recommended against	Conditionally recommended against (first carpometacarpal)	Intra-articular glucocorticoid strongly recommended for knee and hip and conditionally preferred over other intra-articular injections; platelet-rich plasma strongly recommended against for knee and hip	[20]
American Academy of Orthopaedic Surgeons 2021 (OAK, 3rd edition; summary in [21])	"Not recommended for routine use", Moderate strength (downgraded one level)	Not addressed	Not addressed	Corticosteroids may give short-term relief (Moderate, downgraded); platelet-rich plasma may reduce pain and improve function (Limited, downgraded two levels); evidence insufficient to recommend a specific molecular weight	[22,23]
Osteoarthritis Research Society International 2019	Level 1B/Level 2 depending on comorbidity status	Not recommended	Not stated	No platelet-rich plasma recommendation stated	[19]

Published counter-position (rheumatology commentary)	19 of 22 organisations and agencies (86%) neutral or in favour; 7 of 8 agencies with a policy (88%) considered it warranted or reimbursable; 81% of guidelines in one review favourable or neutral	—	—	Notes absence of known systemic effects and a reported association with reduced arthroplasty risk; author overlap with a product-differences meta-analysis and a claims safety analysis	[12,24,31]
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Table 4: Clinical practice guideline positions on intra-articular hyaluronic acid.

Musculoskeletal safety

Severe acute localised reaction — pseudoseptic arthritis or inflammatory flare — is the characteristic serious local event [31]. In a claims analysis of 748,428 patients, inflammation or infection within three days occurred in 0.001% of hylan G-F 20 recipients and 0.002% of others, with no significant between-cohort difference and no stratification by molecular weight or origin [31]. A systematic review of published cases identified 27 patients and 28 knees: 85.2% women, 89.3% having received an avian cross-linked product and onset within 24 hours in 78.6%; differentiation from septic arthritis rests on rapid onset, negative culture and improvement without antibiotics, and a pooled incidence of septic arthritis attributable to HA is unavailable [32]. Label-level contraindications include hypersensitivity to HA, allergy to Gram-positive bacterial proteins, anaphylaxis history, amide-anaesthetic allergy for lidocaine-containing products, local infection and bleeding disorders [67,69,71]; individual label wording must be checked against each insert.

Aesthetic and dermatologic applications

Approved categories and rheology

In the United States, HA fillers are device implants approved for adults aged 22 years or older by category and site, with several anatomical regions and delivery routes that the FDA explicitly recommends against (**Table 12**) [60]. Five approvals since September 2025 extended that list, including two new applicants and the first United States infraorbital indication for resilient HA (**Tables 10, 11 and 14**) [125–131]. Behaviour is described by rheology: the elastic modulus G' reflects firmness and integrates concentration, cross-linking and entanglement; the loss modulus G'' reflects energy dissipated on deformation; $\tan \delta$ is their ratio, values below 1 indicating elastic dominance; cohesivity predicts projection retention; and the swelling factor anticipates initial volumisation, falling as cross-linking rises [33,34]. Cohesivity has no standardised assay, so values obtained at 0.1 Hz and 25 °C are not interchangeable with those at 5 Hz and 0.8% strain [33,34]. Within one internally consistent dataset, G' spans 40 to 1,055 Pa, $\tan \delta$ 1.050 to 0.074 and maximum water uptake under 100% to 700% [34]. This spread, not brand identity, maps product to plane: low- G' , low-swelling gels superficially and in dynamic areas, high- G' gels for supraperiosteal projection at chin, jawline and midface.

Skin boosters versus fillers, and the limits of biostimulation

Skin boosters aim at skin quality rather than volume [42], and the distinction is anatomical as well as commercial: intradermal cross-linked HA improved texture, roughness and dermal thickness whereas subdermal placement of the same material replaced volume without improving texture, with 12–20 mg/mL cited as optimal for skin-quality work [42,44]. Only one product in the category carries a label-defined protocol and annual volume cap (**Table 10**) [74].

Evidence for biostimulation is markedly weaker than for volumisation. A systematic review of injectable HA for facial skin quality included 13 studies by its abstract and 15 in its results, of which only one was randomised [44]. A frequently cited biostimulation report is a six-patient retrospective series in which optical coherence tomography showed progressive collagen-density increase over three months without numerical values, confidence intervals or p-values [43]. 2026 narrative update attributes improvements in hydration, elasticity and texture to neocollagenesis and angiogenesis while giving no pooled effect size and noting absent standardised protocols, its strongest histological anchor being an 11-participant biopsy series [45]. The most studied hybrid-cooperative-complex product (Table 10) rests on nine small, mostly single-centre, manufacturer-funded studies in 278 participants [46], and its post-marketing rate of 0.034% uses a modelled denominator of 1,091,956 patients, not measured exposure [47]. Three further additions test biostimulation. A hybrid of cross-linked HA with calcium hydroxyapatite microspheres reports 82.8% responders at one month sustained to twelve, with neocollagenesis asserted mechanistically rather than measured [117,118]. A polyethylene-glycol-cross-linked, amino-acid-enriched gel — the only non-BDDE chemistry tabulated here — rests on one open-label single-centre study [119,150]. East Asian products supply randomised comparisons the Western literature lacks, including a matched-pairs trial against stabilised HA and a 2026 midface trial in which responders fell from 81.0% at two weeks to 56.1% at 26 weeks [113–116]. The defensible ladder is therefore: volumisation and wrinkle correction supported by premarket-approval-grade randomised evidence; skin-quality and hydration improvement by small, mostly observational studies; neocollagenesis by small histological series without effect estimates; and durable regeneration of youthful dermal architecture by no source examined here.

Duration, reversibility and complications

Durations differ by product and site rather than by class, from a label-defined six months to 24-month cheek data and a label-stated 15–18-month estimated lifetime (Table 5) [67,68,69,70,73]. Reversibility is HA's principal safety advantage, and hyaluronidase dominates removal practice, appearing in 86.7% of 5,945 removal-related device reports [56]. Protocols for emergency and elective dissolution are summarised in (Table 13); occlusion is optimally treated within four hours, and hyaluronidase hypersensitivity is about 0.1%, with bee or wasp venom anaphylaxis a relevant contraindication [37,38].

Vascular occlusion with visual loss defines aesthetic risk. Consensus places filler-related blindness at approximately 0.001%, at or below one per 100,000 syringes (a deliberately conservative 300 cases among 30 million syringes), with cerebral infarction in about 25% of patients sustaining embolic visual compromise [35]; an independent synthesis estimates visual compromise at one to two per 1,000,000 patients with improvement in only 19% [39]. Risk stratification runs from Grade 1 (jawline, lateral cheek, chin) to Grade 4 (glabella, nose, forehead), with the periorbital region at Grade 3 [35]. The comparative effectiveness of aspiration and of cannula versus needle for preventing blindness is unresolved, and blindness has occurred with both [35,37] — so consent must pair a very low probability with a poor prognosis rather than cite either alone.

Delayed-onset reactions are the second characteristic complication, appearing weeks to months after injection with a peak at three to four months at incidences of 0.33%–4% by product family, highest for products approved between 2016 and 2020 containing low-molecular-weight HA (Table 5) [36,40,41]; antibiotics, corticosteroids, 5-fluorouracil and hyaluronidase achieved a 75%–80% response rate across

small non-comparative studies at very low certainty [39]. Two newer signals deserve attention: bone resorption after supraperiosteal injection, reported only for HA fillers [56,69]; and 186 serious-injury reports from unapproved upper-body sites — neck 87.1%, décolletage 10.8%, breast 3.2% — most commonly nodules and rising since 2019 [56].

Metric	Value as reported	Source
Cheek volumisation duration (Vycross technology)	≥1-grade improvement in 86.6% at month 9, 71.5% at month 18, 67.1% at month 24	[67]
Temple augmentation duration	Responders 81.7% at 1 month and 73.3% at 13 months	[67]
Nasolabial fold duration	75% (36/48) improved beyond 36 weeks; mean interval to repeat treatment about 9 months	[68]
Lip augmentation duration	Responders 79.9% at 1 month, 80.5% at 6 months, 56.4% at 12 months (one product); 88% at week 8 and 60% at week 48 (another)	[68,70]
High-G' gel duration	Duration of effect defined as 6 months; safety and effectiveness beyond 1 year not investigated	[69]
Cohesive polydensified matrix product	Mean interval between injections 37.0 weeks (SD 15.6) in open-label extension; beyond 96 weeks not investigated	[71]
Resilient hyaluronic acid product	Label-stated estimated lifetime 15–18 months	[73]
Skin boosters, class-level	Typical duration about 6 months after three treatment sessions	[45]
Filler-related blindness, consensus consent figure	About 0.001%, at or below 1 per 100,000 syringes; working estimate 300 cases among 30 million syringes	[35]
Injection-related visual compromise	1–2 per 1,000,000 patients; improvement in only 19% of cases	[39]
Skin necrosis	About 5 per 1,000 patients; improvement in up to 77%	[39]
Blindness by anatomical site	Nasal region 56.3%, glabella 27.1%, forehead 18.8%; HA implicated in 81.3% of recent cases; retinal circulation must be restored within 60–90 minutes	[35,37]
Late-onset reactions, timing	Weeks to months, peaking between 3 and 4 months	[36]
Late-onset reaction incidence	0.5%–4% for certain fillers composed largely of low-molecular-weight HA; 1.0% per patient in one retrospective series; 0.33% (7/2,139) in one clinic cohort	[36,40,41]
Late-onset events in a pivotal lip trial (≥21 days)	5.4% with the device versus 5.7% with control; all mild or moderate	[70]
Response to treatment of inflammatory events and nodules	75%–80% response with antibiotics, corticosteroids, 5-fluorouracil or hyaluronidase; very low certainty	[39]
Device reports, all-time serious injury (facial and hand filler codes)	17,768 total, including abscess 1,235, nodules 1,038, obstruction or occlusion 986, granulomas 846; 1,478 reports in 2023 against 5,331,426 HA filler procedures that year; incidence cannot be derived	[56]
Filler-removal reports	5,945 device reports; hyaluronidase terms in 86.7%, surgical excision in 12.4%; HA 94.5% of material involved	[56]
Bone resorption after supraperiosteal injection	3 device reports plus as many as 60 cases in 7 publications; reported only for HA fillers; label notes rare reports	[56,69]
Serious events at unapproved upper-body sites	186 unique reports: neck 87.1%, décolletage 10.8%, breast 3.2%; nodules most common; increasing since 2019	[56]
Hybrid cooperative complex post-marketing surveillance	371 adverse events (0.034%) against a modelled exposure of 1,091,956 patients; 1 embolism, 1 vascular occlusion	[47]

Table 5: Aesthetic hyaluronic acid: label-derived duration and safety metrics.

Other regenerative and therapeutic uses

(Table 6) classifies these indications, and two patterns recur. First, approved routine use does not imply

demonstrated efficacy: a Cochrane review of HA dressings in 12 trials and 1,108 participants graded every outcome very low certainty and found no comparison showing a clear healing benefit [48,49], while for dry eye pooled Schirmer I favoured HA (SMD 0.238; 95% CI 0.107–0.369) but tear break-up time favoured comparators, an effect that disappeared on sensitivity analysis [50]. Second, positive uncontrolled results repeatedly fail to survive a comparator: a randomised pilot of a vaginal HA insert versus vaginal estradiol found no meaningful difference at 12 weeks ($p = 0.81$) [51]; intravesical instillation for bladder pain syndrome is off-label with uncontrolled data only [53]; and the most recent randomised trial in lateral epicondylitis is uninterpretable because 9 of 17 saline participants did not complete follow-up [52].

Indication and named products	Status	Best available evidence	Tier	Verified price (USD; type; date)	Sources
Chronic wounds (pressure, diabetic foot and leg ulcers) — Hyalomatrix (HYAFF-11 non-woven pad with silicone membrane), Bionect 0.2% cream/gel, ialuset 0.2% cream and 0.05% impregnated dressing, Hyiodine (HA 1.5% with iodine 0.1%)	Approved routine use as dressings and topical agents (US 510(k); EU CE)	12 randomised trials, 1,108 participants; no comparison showed clear healing benefit; every outcome very low certainty. Product-level support is labelling plus one clinical evaluation of the HA–iodine complex	Tier 1–2	Bionect 0.2%, 25 g; average retail 200.75, discount 150.59 [CASH] , updated 16 May 2026. UK tariff: Hydromol Relief 100 mL 12.19; Xclair 50 g 23.03 [ASP] , Sep 2026. Hyalomatrix, ialuset, Hyiodine n.a.	[48,49,122,135,152,153,156,161]
Dry eye disease — NHS-listed HA tear substitutes (Hylo-Tear 0.1%, Hylo-Forte 0.2%, Hyabak 0.15%, Vismed range, Thealoz Duo, Artelac Rebalance, Optive Fusion) and HA eye ointments (AquaNocte, eyenite)	Approved routine use as lubricants; reimbursed UK appliances	18 studies, 10 randomised trials meta-analysed; Schirmer I favoured HA, tear break-up time did not; differences under 1 mm and 1 second. Laboratory analysis of 37 European tear substitutes measured HA at 79%–104% of the label claim, and one product with no claim measured 0.28%	Tier 2	10 mL bottles: Artelac Rebalance 5.42; Optive Fusion 10.15; Hyabak 10.82; Hylo-Tear 11.51; Hylo-Forte 12.87. Eye ointment 5 g 9.47. Portfolio range 3.36–10.30 GBP-derived [ASP — NHS basic price] , Sep 2026	[50,108,156]

Genitourinary syndrome of menopause — HyaloGYN vaginal hydrating gel, Hyalofemme, Desirial (intramucosal cross-linked HA 19 mg/g)	Gels approved as lubricant/moisturiser devices; intramucosal injection is a class III device use	Randomised pilot, 49 participants: no meaningful difference versus vaginal estradiol at 12 weeks ($p = 0.81$). The one fetched study measuring a structural endpoint found total vaginal mucosal thickness unchanged (213.65 versus 212.33; $p = 0.5949$)	Tier 2; biostimulation not supported	Hyalofemme 30 g: 6.72 [ASP], Sep 2026. HyaloGYN, Desirial n.a.	[51,121,136,156]
Bladder pain syndrome, radiation cystitis and recurrent urinary tract infection — iAluRil (HA 800 mg + chondroitin sulfate 1 g/50 mL), Hyacyst 40 mg and 120 mg/50 mL, Cystistat 40 mg/50 mL	Off-label or device-regulated instillation, region-dependent	Uncontrolled multicentre trial, 54 patients, 75% complete response in the bladder pain group; the MISTIC randomised controlled trial tested HA plus chondroitin sulfate for prevention of radiation cystitis, so its effect cannot be attributed to HA alone	Tier 1–2	iAluRil 50 mL 119.20; Hyacyst 50 mL 94.82 (both strengths) [ASP — NHS basic price], Sep 2026. Cystistat n.a.	[53,120,151,156]
Lateral epicondylitis	Investigational	Randomised trial invalidated as a controlled comparison by control-arm attrition; large within-group improvement only	Tier 1	n.a.	[52]
Cataract and anterior-segment surgery — ophthalmic viscosurgical devices: Healon PRO 1%, ProVisc 1%, Viscoat (3% HA with 4% chondroitin sulfate), DisCoVisc, Amvisc/Amvisc Plus, ClearVisc (2.5% HA with sorbitol, 750 kDa), StableVisc (1%, 2.1 MDa) and the TotalVisc co-pack	Approved routine use; US class III premarket approval (ClearVisc 2021, StableVisc 2023)	Cohesive and dispersive devices spanning 10–30 mg/mL and 7.5×10^5 – 3.2×10^6 Da. In 36 randomised trials of 3,893 subjects, day-1 intraocular pressure rose significantly (Healon SMD 0.37, 95% CI 0.07–0.67; Viscoat 0.29, 0.13–0.45); corneal oedema 0.6%–2.5%	Tier 1 (space maintenance and endothelial protection)	n.a.	[112,124,133,134]

Faecal incontinence (Solesta) and paediatric vesicoureteral reflux (Deflux) — dextranomer microspheres 50 mg/mL with stabilised sodium hyaluronate 15 mg/mL	Approved; US premarket approval 2011 (Solesta) and September 2001 (Deflux)	International multicentre double-blind sham-controlled randomised trial, 206 patients (136 active, 70 sham), with responder criteria at 6 and 12 months both required for success; proctalgia 14% versus 3%, fever 8% versus 0%, rectal haemorrhage 7% versus 1%, plus one prostatic and one rectal abscess	Tier 1 (bulking)	Solesta, four-syringe treatment: 754.49–1,005.99 [ASP — 2024 Medicare unadjusted allowed amount]. Deflux n.a.	[124,132,157]
Post-surgical adhesion prevention — Seprafilm (sodium hyaluronate with carboxymethylcellulose membrane); ex-US Guardix-sol, MateRegen and HyalRegen cross-linked gels	Approved (US premarket approval P950034); ex-US devices	13 randomised trials, 3,665 patients: adhesive small-bowel obstruction 3.0% versus 5.9% (RR 0.53, 95% CI 0.38–0.73) but anastomotic leak 3.1% versus 1.6% (RR 1.85, 95% CI 1.15–3.00). Ex-US randomised trials of intrauterine and abdominopelvic gels report adhesion and menstrual-pattern endpoints, not tissue restoration. A 15 March 2024 US recall records distribution "without proper regulatory approval"	Tier 1–2 (barrier), with an explicit harm signal	Seprafilm single 13 × 15 cm sheet: 110.00 [DIST], accessed 9 Sep 2026. Ex-US gels n.a.	[124,139,148,161]
Cartilage repair with cells or marrow concentrate — Hyalofast (HYAFF scaffold; CE-marked, more than 35,000 patients treated since 2009), Chondrotissue (polyglycolic acid with hyaluronan), Agili-C	Investigational in the US; final premarket-approval module for Hyalofast filed 31 October 2025	Uncontrolled 7-patient phase I/II with hyaline-like repair; pivotal randomised FastTRACK trial failed both co-primary endpoints; Hyalofast comparative data are non-randomised (21 versus 25 knees; 19 versus 24 patients); the Chondrotissue randomised trial has 24 patients and a composite scaffold; the FDA review states evidence was lacking for Agili-C	Tier 1, not Tier 4	n.a.	[54,55,124,149]

Withdrawn or discontinued applications — Zuidex (dextranomer/HA urethral bulking), Macrolane (large-volume body and breast)	Zuidex withdrawn; Macrolane breast use discontinued	Zuidex versus bladder-neck collagen in 344 women: injection-site complications 16% versus 0% (RR 37.78, 95% CI 2.34–610.12), sterile abscess 8.4%, and 28 of 36 periurethral collections requiring secondary drainage. Macrolane breast series (n = 194) major adverse events 8.7%; in a 20-patient complication series every patient had lumpiness and at least 85% of filler was surgically removed	Safety precedent	n.a.	[124]
Hydrogels, scaffolds and bioinks	Preclinical / investigational	Tunable cross-linked platforms for cell and drug delivery and three-dimensional printing	Tier 1	n.a.	[5,7]
HA–Chitlac composite / Arty-Duo	Preclinical / investigational	Lactose-modified chitosan combined with HA showed anti-inflammatory and cartilage-repair signals in experimental osteoarthritis; Arty-Duo was evaluated in a rat-knee model, not established clinical care	Tier 1	n.a.	[106]
Hyaff-11 scaffold	Investigational regenerative scaffold	Three-dimensional biodegradable HA-based scaffold used for human chondrocyte culture and autologous chondrocyte implantation; the cited evidence does not establish efficacy for routine osteoarthritis treatment	Tier 1, not Tier 4	n.a.	[106]

Oncology caution (not an indication)	—	Excess HA production and HAS2 activity promote cancer-stem-cell signatures and tumour progression; CD44 overexpression associated with poor prognosis in several carcinomas	Safety signal	n.a.	[4,5,8]
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Table 6: Other hyaluronic acid indications: named products, approval status, evidence tier and verified price (14 categories). Prices are labelled by type with date and unit; "n.a." indicates that no defensible current price was identified. Prices are not evidence of effectiveness.

(Table 6) now names the products behind each use and adds four categories that discipline the regeneration claim. Ophthalmic viscosurgical devices (10–30 mg/mL; 7.5×10^5 – 3.2×10^6 Da) are indispensable surgical adjuncts whose characteristic harm is transient intraocular-pressure elevation [112,124]; stabilised HA with dextranomer is approved for faecal incontinence on a sham-controlled trial and for paediatric vesicoureteral reflux, acting purely by bulking [132]; the most studied adhesion barrier reduced adhesive small-bowel obstruction (3.0% versus 5.9%; RR 0.53, 95% CI 0.38–0.73) but increased anastomotic leak (3.1% versus 1.6%; RR 1.85, 95% CI 1.15–3.00) across 13 trials [124]; a cross-linked vulvovaginal gel sold for biostimulation produced no significant change in mucosal thickness ($p = 0.5949$) [121]; and two applications were withdrawn or discontinued after sterile abscess in 8.4% of 344 randomised women and surgical removal of $\geq 85\%$ of a large-volume breast implant in every patient of a 20-patient series [124].

Product characteristics, commercial landscape and pricing

(Tables 8 and 9) present 34 musculoskeletal HA products and (Tables 10 and 11) present 33 aesthetic products, with "n.a." where data are unavailable; Chitlac/Arty-Duo and Hyaff-11 are classified separately as experimental technologies [106]. Opus 3F and Osteonil Plus illustrate contrasting non-animal strategies — three molecular-weight fractions with mixed cross-linking versus 40 mg/2 mL of 1–2 MDa HA with mannitol — and no head-to-head trial was identified [101–104]. Medicare course costs calculated from the payment limits effective 1 July 2026 span USD 186.90 to USD 870.29, a 4.7-fold range, and are provisional by design: the preliminary October–December 2026 file, published on 8 September 2026, alters twelve of the thirteen HA billing codes [154,155]. European retail prices are far lower — USD 97.56 per 60 mg/4 mL hip syringe and USD 109.06 per three-syringe pack of a 32 mg/2 mL product, both converted from euro at the 8 September 2026 reference rate, and USD 224.13 for a tendon-labelled syringe listed in dollars [158,159] — while distributor listings for the newly approved aesthetic products span USD 69.00 to USD 349.00 per unit against a patient-paid HA-filler average of USD 715 [90,160]. A cross-border Osteonil listing was USD 99.36 per syringe [105], while public prices for several products outside the United States were not established. Prices fluctuate and do not demonstrate effectiveness.

#	Brand (manufacturer/labeller)	HA source	Concentration and dose per injection	Average molecular weight	Architecture	Regimen	US regulatory status and HCPCS code	Sources
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1	Hyalgan (Fidia Pharma USA)	Avian, rooster comb	10 mg/mL; 2 mL	500–730 kDa	Linear	3–5 weekly (payer policy lists 5)	Class III device, premarket approval; first intra-articular HA approved as a Class III device for knee osteoarthritis in the US; J7321	[18,57]
2	Supartz / Supartz FX (Bioventus)	Avian, rooster comb	10 mg/mL; 2.5 mL	620–1,170 kDa	Linear	5 weekly (policy 3–5)	Device, approval year 2001; formerly Artz/Artzal; J7321	[18,57]
3	GenVisc 850 (OrthogenRx)	Bacterial fermentation	10 mg/mL; 2.5 mL (25 mg)	620–1,170 kDa	Linear	5 weekly (policy 3–5)	Device; approved on equivalence to Supartz FX by chemical composition, physical characteristics and non-inferior clinical performance; J7320	[18,57,84]
4	TriVisc (OrthogenRx)	n.a.	n.a.	n.a.	n.a.	3- or 5-injection series offered	Device; J7329	[66,87]
5	Orthovisc (Anika Therapeutics; also listed as DePuy Synthes Mitek)	Bacterial fermentation	15 mg/mL; 2 mL (30 mg)	1,000–2,900 kDa	Linear	3–4 weekly	Device, approval year 2004; J7324	[18,57,80]
6	Monovisc (DePuy Synthes Mitek; Anika technology)	Bacterial fermentation	22 mg/mL; 4 mL (88 mg)	1,000–2,900 kDa	Cross-linked, hydrophobic; same HA grade as Orthovisc	Single injection	Device, approval year 2014; J7327	[18,57]
7	Euflexxa (Ferring Pharmaceuticals)	Bacterial fermentation (BioHA)	10 mg/mL; 2 mL (20 mg)	2,400–3,600 kDa	Linear (straight chain)	3weekly	Device, approval stated as 2004/2011; J7323	[18,57,78]
8	Gelsyn-3 / Sinovial (Bioventus)	Bacterial fermentation	8.4 mg/mL; 2 mL (16.8 mg)	1,400–2,100 kDa	Not stated	3weekly	Device; J7328	[18,57,79]
9	Synvisc, hylan G-F 20 (Genzyme Biosurgery)	Avian, rooster comb	8 mg/mL; 2 mL (16 mg)	6,000 kDa	Cross-linked: 80 hylan A to 20 hylan B	3weekly	Device, approval year 1997; J7325	[18,57]
10	Synvisc-One (Genzyme Biosurgery)	Avian, rooster comb	8 mg/mL; 6 mL (48 mg)	6,000 kDa	Cross-linked hylan G-F 20	Single injection	Device, approval year 2009; J7325	[18,57,77]
11	Durolane, NASHA (Bioventus)	Bacterial fermentation, non-animal	20 mg/mL; 3 mL (60 mg)	100,000 kDa; described as ultra-high molecular weight, >100,000 kDa	Linear chains stabilised by about 1% synthetic cross-links in a three-dimensional gel	Single injection	Device, approval year 2017; J7318	[17,18,29,57,83]
12	Gel-One (Zimmer Biomet)	Avian, highly purified from chicken combs	1% solution, 10 mg/mL; 3 mL (30 mg)	Not reportable for the cross-linked formulation	100% cross-linked hydrogel by photogelation	Single injection	Device, approval year 2011; J7326	[18,57,75,82]
13	Hymovis, HYADD4-G (Fidia Pharma USA)	Bacterial fermentation	8 mg/mL; 3 mL (24 mg)	500–730 kDa	Non-cross-linked hexadecylamide derivative of hyaluronan	2 weekly injections	Device, approval year 2015; J7322	[18,57,85]
14	Hymovis One (Fidia Pharma USA)	Bacterial fermentation (same platform)	n.a.	n.a.	n.a.	Single injection	Device; J7322	[57]
15	Triluron (Fidia Pharma USA)	n.a.	20 mg / 2 mL	n.a.	n.a.	3 injections	Device; NDC 89122-0879-01; J7332	[57,88]
16	Synjoynt (Teva Pharmaceuticals USA)	n.a.	20 mg / 2 mL prefilled syringe	Approximately 2,500 kDa	Linear sodium hyaluronate	3 weekly injections	FDA Class III device; J7331	[57,100]

17	Visco-3 (Zimmer)	n.a. (shares a J-code with avian-derived products)	25 mg / 2.5 mL	n.a.	n.a.	3 syringes per course	Device; no generic version; J7321	[57,85]
18	Cingal (Anika Therapeutics)	n.a.	88 mg/4 mL HA plus 18 mg/4 mL triamcinolone hexacetonide; one 4 mL prefilled syringe	n.a.	Cross-linked HA platform; not stated on the fetched page	Single injection	Not listed in the FDA-approved viscosupplement J-code set or the April 2026 payment file; US approval status n.a.; implicated in a published pseudoseptic arthritis index case; HCPCS n.a.	[32,88]
19	Opus 3F (DMC Equipamentos, Brazil)	Synthetic/non-animal	Concentration and total HA dose n.a.; 2 mL syringe	Manufacturer reports 5.4 MDa overall and low-, medium- and high-molecular-weight fractions; fraction-specific values n.a.	Mixed: low-molecular-weight non-cross-linked fraction plus cross-linked medium- and high-molecular-weight fractions	Manufacturer does not publish a fixed regimen; packs contain 1 or up to 3 syringes	ANVISA registration 80030810176; US FDA/HCPCS status n.a.	[101,102]
20	Osteonil Plus / Ostenil Plus (TRB Pharma/TRB Chemedica)	Bacterial fermentation; non-animal	20 mg/mL; 2 mL (40 mg); includes 0.5% mannitol (10 mg/2 mL)	1,000–2,000 kDa	Cross-linking not disclosed; presented as sodium hyaluronate solution stabilised against free radicals by mannitol	Intra-articular: 1–3 weekly injections; Brazilian label also permits 2 weekly periarticular injections	ANVISA registration 80149050006; EU Class III medical-device certificate; US FDA/HCPCS status n.a.	[103,104]
21	Synolis VA	Biofermentation	HA 20 mg (2%) plus sorbitol 40 mg (4%); volume n.a. in the source table	2.1 MDa	Cross-linking n.a.; HA–sorbitol formulation	Knee or hip osteoarthritis; regimen n.a.	Regulatory status n.a.	[106]
22	RenehaVis	Biofermentation	Low-molecular-weight HA 15.4 mg (2.2%) plus high-molecular-weight HA 7 mg (1%); volume n.a.	<1 MDa and 2 MDa fractions	Dual-molecular-weight formulation; cross-linking n.a.	Knee or hip osteoarthritis; regimen n.a.	Regulatory status n.a.	[106]
23	SportVis	Biofermentation	12 mg (1%); volume n.a.	Not reported	Cross-linking n.a.	Soft-tissue/tendon injuries; not listed as an osteoarthritis viscosupplement	Regulatory status n.a.	[106]
24	Ostenil	Biofermentation	20 mg (1%); volume n.a. in the source table	1–2 MDa	Cross-linking n.a.	Shoulder, hip and knee osteoarthritis; regimen n.a.	Regulatory status n.a.	[106]
25	Orthovisc mini	Biofermentation	15 mg (1.5%); volume n.a. in the source table	1.4 MDa	Linear/cross-linking status n.a. in the cited table	Small joints; regimen n.a.	Regulatory status n.a.	[106]

26	ARTHRUM H 2% / ARTHRUM visc 75 / ARTHRUM HCS (LCA Pharmaceutical, Chartres, France)	n.a. (not stated in the labels)	H 2%: 20 mg/mL, 40 mg/2 mL visc 75: 25 mg/mL, 75 mg/3 mL HCS: 20 mg/mL, 40 mg HA + 40 mg chondroitin sulfate per 2 mL	2,400 kDa (H 2%, visc 75); 2.8 × 10 ⁶ Da (HCS)	Non-cross- linked; HCS adds chondroitin sulfate and states components are "not chemically modified"	H 2% and HCS: 1 injection weekly × 3. visc 75: single injection	Not FDA-approved; CE- marked class III device (HCS CE mark 2010); no HCPCS code	[110,141]
27	Adant / Adant Dispo / Adant Plus (Meiji Pharma Spain)	Bacterial fermentatio n	Adant: 10 mg/mL, 25 mg/2.5 mL Adant Plus: 20 mg/mL, 98 mg per syringe	620–1,170 kDa (Supartz- equivalent formulation)	Linear, non- cross-linked	Adant: 1 injection weekly × 5, one cycle per year. Adant Plus: single injection, usually annual	Not FDA-approved under this name; the same formulation family is marketed in the US as GenVisc 850 (row 3); no HCPCS code	[18,142]
28	Artz / Artz Dispo / Artzal (Seikagaku)	Avian, rooster comb	10 mg/mL; 25 mg/2.5 mL	600–1,200 kDa	Non-cross- linked	1 injection weekly × 5	Historical US brand name of the Supartz platform (row 2); marketed in Japan and internationally; billed in the US as Supartz FX under J7321	[18,107]
29	Hyalubrix / Hyalubrix 60, also HyalOne (Fidia Farmaceutici)	n.a.	15 mg/mL; 30 mg/2 mL and 60 mg/4 mL	1,500–2,000 kDa	Non-modified (not cross- linked)	2 mL: 1 injection weekly × 3. 4 mL presentation regimen not stated in the fetched sources; hip administration requires imaging guidance	Not FDA-approved; EU device; no HCPCS code	[123,124]
30	Sinovial Forte 1.6% / Sinovial One 2% / Sinovial HL (IBSA Farmaceutici Italia)	Fermentati on, without chemical modificatio n	Forte: 32 mg/2 mL (1.6%). One: 50 mg/2.5 mL (2%). HL: 32 mg high- molecular- weight plus 32 mg low- molecular- weight HA per 2 mL	800–1,200 kDa (Forte, One); fractions not quantified for HL	Not chemically modified; HL is a thermally produced hybrid complex of high- and low- molecular- weight chains	Forte and One: single injection. HL: maximum 3 injections by severity	Not FDA-approved at these concentrations; the 0.8% formulation of the same platform is the FDA- approved Gelsyn-3 device (row 8, premarket approval P110005). Trade-name variants of the platform include Intragel, Jointex, Yaral and Gony Alert MD; no HCPCS code	[109,143,144]
31	Hyruan ONE (LG Chem)	Non-animal	20 mg/mL; 60 mg/3 mL	High molecular weight; numeric value not stated	Cross-linked with 1,4- butanediol diglycidyl ether	Single injection	Approved in South Korea since 2013 and CE-marked 2014; not FDA-approved; no HCPCS code	[111]
32	OSTENIL TENDON (TRB Chemedica)	n.a.	20 mg/mL (2.0%); 40 mg/2 mL	n.a.	Mannitol added to stabilise the hyaluronate chains; cross- linking not stated	Peritendinous or intrasheath injection once weekly × 2 for named tendons (Achilles, epicondylus humeri, supraspinatus, patellar, peroneal, biceps brachii) and the iliotibial band; imaging guidance advised	EU/UK device with published summary of product characteristics; not FDA-approved; no HCPCS code	[145]
33	VISCOSEAL / VISCOSEAL SYRINGE (TRB Chemedica)	Fermentati on-derived sodium hyaluronate	5.0 mg/mL (0.5%); 10 mL	n.a.	Cross-linking not stated	Single instillation at the end of arthroscopy, after the normal irrigation procedure, as a synovial-fluid substitute	EU/UK device; not FDA- approved; no HCPCS code	[146]

3 4	OSTENIL MINI (TRB Chemedica)	n.a.	10.0 mg/mL; 10 mg/1 mL	n.a.	Cross-linking not stated	Small synovial joints (lumbar facet, thumb saddle, interphalangeal, first metatarsophalangeal, temporomandibular); 1–3 weekly injections, cycles repeatable	EU/UK device; not FDA- approved; no HCPCS code	[147]
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Table 8: Musculoskeletal hyaluronic acid products: characteristics (34 products).

Most entries are intra-articular viscosupplements; SportVis and Ostenil Tendon are tendon-directed, Viscoseal is a post-arthroscopy synovial-fluid substitute, and Ostenil Mini and Orthovisc mini are small-joint presentations. Rows 26–34 are marketed outside the United States and were added in this revision. Fields not verifiable from the cited sources are entered as "n.a." and must not be inferred. Brands are listed for product-literacy purposes only and are not endorsed.

#	Brand	[ASP]	[ASP- calc] course	[DIST] / [CASH] / [PATIENT]	Strengths	Limitations	Sources
1	Hyalgan	70.282 per dose (J7321)	5 doses = 351.41; 3 doses = 210.85	[CASH] average retail 829.10– 845.98; discount price 446.81 for 3 syringes (updated 4 Sep 2026)	Longest US track record; first approved intra- articular HA; low molecular weight well characterised	Avian origin with higher pooled acute flare-up rate; 3–5 visits; molecular weight below the more favourable band; reported as not covered by most plans	[12,66,84]
2	Supartz / Supartz FX	70.282 per dose (J7321)	5 doses = 351.41	[DIST] list 165.95, sale 125.00 per 2.5 mL syringe; [CASH] average retail 284.33, discount 247.30 per syringe (updated 21 May 2026)	Lowest single- syringe distributor price in this table; widely covered per the retail source	Avian; 5 injections; molecular weight below the ≥3,000 kDa band	[66,81,84]
3	GenVisc 850	3.808 per mg (J7320)	25 mg = 95.20 per syringe; 5 syringes = 476.00	[CASH] average retail 590.68, discount 411.24 per syringe (updated 10 May 2026); [PATIENT] manufacturer direct- pay 97 per syringe	Bacterial- fermentation origin; direct-pay programme far below retail	5 injections; approved on equivalence to an avian product despite differing origin; direct- pay requires prescription routing and prepayment	[66,84,87]
4	TriVisc	3.036 per mg (J7329)	n.a. (labelled dose not confirmed)	[PATIENT] direct-pay 97 per syringe; three-injection regimen stated at 291	Lowest transparent patient-facing series price identified	Product properties n.a.; no independent efficacy data retrieved	[66,87]
5	Orthovisc	100.331 per dose (J7324)	3 doses = 300.99; 4 doses = 401.32	[DIST] list 899.95, sale 680.00 per 2 mL syringe; [CASH] average retail 1,971.25 (a second page of the same vendor shows 2,199.10), discount 1,454.52 for 3 syringes (updated 28 May 2026)	Bacterial fermentation; molecular-weight range extends into the higher-efficacy band; flexible 3–4 injections	Multi-visit; internally inconsistent retail averages on one vendor's own pages illustrate the unreliability of consumer price data	[66,80,84]
6	Monovisc	565.275 per dose (J7327), the highest per-dose limit in the class	1 dose = 565.28	[CASH] average retail 1,943.41, discount 1,521.05 for one 4 mL syringe (updated 20 May 2026)	Single injection; cross-linked; delivers HA mass comparable to a three-injection course of its linear counterpart	Highest single-dose reimbursement and cash price in the class; hydrophobic cross- linking may alter local tolerability	[18,66,84]

7	Euflexxa	98.137 per dose (J7323)	3 doses = 294.41	[DIST] list 1,795.95, sale 1,455.00 per box of 3 syringes; [CASH] average retail 1,393.30, discount 1,099.59 for 3 syringes (updated 20 May 2026)	Bacterial fermentation; highest linear molecular weight in the US class, reaching the favourable band at its upper end	3 visits; distributor box price about 6.1 times the calculated course cost	[66,78,84]
8	Gelsyn-3	0.584 per 0.1 mg (J7328)	16.8 mg = 98.11 per syringe; 3 syringes = 294.34	[DIST] list 675.00, sale 549.00 per 16.8 mg/2 mL syringe	Lowest calculated course cost among multi-injection bacterial-fermentation products	Lowest total HA mass per course (50.4 mg), limiting comparability; cross-linking status not stated	[66,79]
9	Synvisc	6.018 per mg (J7325)	3 × 16 mg = 288.86	[DIST] only unverified international/import listings retrieved; treat as unverified	6,000 kDa cross-linked; most extensively studied single product; superior to two comparators on WOMAC in one 227-patient study	Avian; implicated in 89.3% of published pseudoseptic-arthritis knees; inferior to stabilised ultra-high-molecular-weight HA on 6-month pain in a 182-knee comparison	[13,17,32,66]
10	Synvisc-One	6.018 per mg (J7325)	48 mg = 288.86	[DIST] list 2,295.00, sale 1,650.00 per 6 mL syringe	Single injection delivering the full 48 mg dose	Avian; distributor list price about 7.9 times the calculated course cost (5.7 times at the sale price), the widest acquisition-to-reimbursement gap in this table	[66,77]
11	Durolane	6.239 per mg (J7318)	60 mg = 374.34	[DIST] 1,107.99 per 60 mg/3 mL syringe	Single injection; ultra-high molecular weight; 4-week intra-articular half-life; superiority over methylprednisolone at week 26; matched allogeneic mesenchymal stromal cells at 12 months	Highest local adverse-effect rate by molecular-weight class in hip osteoarthritis (37.5%); inferior to hylan G-F 20 on WOMAC in one comparison; classified as a specialty medication with no published retail price	[13,17,27,66,83]
12	Gel-One	533.592 per dose (J7326)	1 dose = 533.59	[DIST] list 1,995.95, sale 1,425.00 per 3 mL syringe	Single low-volume injection of a fully cross-linked photo-gelation hydrogel	Avian (chicken combs); second-highest per-dose limit; no molecular weight reportable	[18,66,82]
13	Hymovis	18.131 per mg (J7322)	24 mg = 435.14 per injection ; 2 injections = 870.29	[CASH] approximate retail 2,106.69, discount 980.00 for 2 syringes of 24 mg/3 mL	Only two injections; chemically modified non-cross-linked hydrogel; bacterial fermentation	Highest calculated course cost in this table; low molecular weight; no generic alternative	[18,66,85]
14	Hymovis One	18.131 per mg (J7322)	n.a. (dose not confirmed)	n.a.	Single-injection version of the same platform	Product specification not published on any page examined	[57,66]
15	Triluron	10.430 per mg (J7332)	20 mg = 208.60 per injection ; 3 injections = 625.80	[DIST] distributor page displays a gated price; listed price n.a.	Established J-code and defined three-injection regimen	Source, molecular weight and cross-linking n.a.; no transparent acquisition price obtainable	[66,88]

16	Synjoiynt	3.115 per mg (J7331)	20 mg = 62.30 per injection ; 3 injections = 186.90	[PATIENT] 880 for a bundled "Synjoiynt injection" procedure; the source does not state whether this covers one syringe, a package or a procedure including professional fee	Lowest calculated course cost in this table	Product specification n.a.; only an undifferentiated bundled price is obtainable	[66,86]
17	Visco-3	70.282 per dose (J7321)	3 doses = 210.85	[CASH] typical cash price 466.02 for 3 syringes of 25 mg/2.5 mL; discount 280.73	Shares the low J7321 per-dose rate; branded with no generic	Source, molecular weight and cross-linking n.a.; shares a J-code with two avian products, obscuring product-level cost accounting	[66,85]
18	Cingal	n.a. (no J-code in the July–September or October–December 2026 files)	n.a.	[DIST] 259.00 per unit for one 4 mL prefilled syringe	Combines cross-linked HA with a corticosteroid, potentially pairing rapid corticosteroid onset with HA durability	US approval status n.a.; vendor page does not state FDA approval and lists inconsistent presentations; implicated in a published pseudoseptic-arthritis index case 12 hours after a first injection	[32,66,88]
19	Opus 3F	n.a. (no US HCPCS code identified)	n.a.	[DIST]/[CASH]/[PATIENT] n.a.; no transparent public price identified	Non-animal; combines three molecular-weight fractions and cross-linked/non-cross-linked phases; ANVISA-registered; 2 mL presentation	HA concentration, fraction-specific molecular weights, fixed regimen and acquisition price not publicly disclosed in the retrieved manufacturer material; no product-specific comparative trial identified	[101,102]
20	Osteonil Plus / Ostenil Plus	n.a. (no US HCPCS code identified)	n.a.	[DIST] USD 99.36 per 40 mg/2 mL syringe on an international supplier page; out of stock when accessed in September 2026	Non-animal fermentation; 40 mg in 2 mL; mannitol may protect HA chains from free-radical degradation; ANVISA-registered; label covers large joints and periarticular tendon use	Lower molecular-weight band than Opus 3F; 1–3 joint injections may be required; no head-to-head trial with Opus 3F identified; cross-border price excludes professional fees and may not reflect authorised local distribution	[103–105]
21	Synolis VA	n.a.	n.a.	n.a.; no verifiable USD price identified for this review	Biofermentation-derived 2.1 MDa HA with sorbitol; knee and hip indications listed by Costa et al.	Regimen, regulatory status and comparative product-specific efficacy not reported in the source table	[106]
22	RenehaVis	n.a.	n.a.	n.a.; no verifiable USD price identified for this review	Combines <1 MDa and 2 MDa HA fractions; knee and hip indications listed	Regimen, regulatory status and comparative product-specific efficacy not reported in the source table	[106]
23	SportVis	n.a.	n.a.	n.a.; no verifiable USD price identified for this review	Tendon-directed HA product broadening the comparison beyond intra-articular use	Not an equivalent knee-osteoarthritis viscosupplement; molecular weight, regimen and regulatory status not reported in the source table	[106]
24	Ostenil	n.a.	n.a.	n.a.; no verifiable USD price identified for this review	Biofermentation-derived 1–2 MDa HA; shoulder, hip and knee indications listed	Distinct lower-concentration product from Osteonil/Ostenil Plus; regimen and regulatory status not reported in the source table	[106]
25	Orthovisc mini	n.a.	n.a.	n.a.; no verifiable USD price identified for this review	15 mg biofermentation-derived HA, 1.4 MDa, intended for small joints	Should not be extrapolated from knee-specific Orthovisc evidence; regimen, regulatory status and comparative efficacy not reported in the source table	[106]

26	ARTHRUM H 2% / visc 75 / HCS	n.a. (not FDA-approved)	n.a.	n.a.; no defensible current USD listing identified	The only family in this table with a dedicated product-family meta-analysis: strict OMERACT-OARSI response 68.4% at 3–4 months and 76.8% at 6 months for the 2% presentation, 88.6% and 91.2% in an open study of the single-injection 2.5% presentation, with WOMAC A mean difference 25.18 (95% CI 21.02–29.34) at 6 months; a chondroitin-sulfate variant is available	Comparative superiority of the chondroitin-sulfate variant was significant only at the earliest time point (WOMAC A difference 4.1, $p = 0.045$) and lost thereafter; the single-injection evidence is open-label; minor adverse events 6.5%	[110,141]
27	Adant / Adant Plus	n.a. under this brand (the same formulation family is billed in the US as GenVisc 850, J7320)	n.a.	n.a.; no defensible current USD listing identified	The AMELIA trial is the longest randomised repeated-cycle dataset in viscosupplementation, with OARSI responder rates significantly above placebo from 14 months ($p = 0.030$) to 40 months ($p = 0.004$) in 306 patients; comparable to a cross-linked single injection in a 41-patient comparison	Five injections per cycle; label warns of rash, urticaria and, very rarely, anaphylactic reactions; no transparent USD acquisition price	[18,142]
28	Artz / Artz Dispo / Artzal	Billed in the US as Supartz FX (70.282 per dose, J7321)	5 doses = 351.41	n.a. for the Artz brand	Head-to-head randomised data: in 246 patients Artzal, hylan G-F 20 and placebo all improved with no between-group difference through 26 weeks, and a stabilised single injection was non-inferior to ARTZ on WOMAC pain at 18 and 26 weeks ($n = 349$)	Avian origin; five injections; the trials most often cited as "HA versus HA" comparisons rest on this platform, so its null results temper class-level claims	[18,107]
29	Hyalubrix / Hyalubrix 60 (HyalOne)	n.a. (not FDA-approved)	n.a.	[CASH] 97.56 per 60 mg/4 mL syringe (EUR 84.00 at the 8 Sep 2026 reference rate; listed as reduced from EUR 142.00), accessed 9 Sep 2026	Best-documented non-modified high-molecular-weight product for hip osteoarthritis, included in 5 randomised hip trials; the cheapest verifiable per-syringe price of any product in this table	Pain flare 7% versus 2.4% for placebo in pooled hip trials, and an overall adverse-event rate of 29.0% (range 0–49.7%) across 9 hip randomised trials; cross-border retail price excludes professional fees	[123,124,158,159]

30	Sinovial Forte 1.6% / One 2% / HL	n.a. at these concentrations (the 0.8% formulation of the platform is Gelsyn-3, J7328)	n.a.	[CASH] Sinovial Forte 109.06 per pack of three 32 mg/2 mL syringes, about 36.35 per syringe (EUR 93.90 at the 8 Sep 2026 reference rate), accessed 9 Sep 2026; Sinovial One and HL n.a.	One European platform documented by a published EU-MDR summary of safety and clinical performance, spanning three concentrations plus a high-plus-low-molecular-weight hybrid; per-syringe cost about one-third of the lowest US distributor price	No product-specific randomised trial was retrieved for the 1.6%, 2% or hybrid formulations; the hybrid's in-vitro platelet-rich-plasma compatibility data are not clinical evidence; trade-name proliferation obscures product identity	[109,143,144,158,159]
31	Hyruan ONE	n.a. (not FDA-approved)	n.a.	n.a.; no defensible current USD listing identified	Cross-linked single injection tested against a stabilised ultra-high-molecular-weight comparator in a prospective randomised multicentre non-inferiority trial in European patients	Active-controlled design without a placebo or saline arm; molecular weight not numerically disclosed	[111]
32	OSTENIL TENDON	n.a. (not FDA-approved)	n.a.	[CASH] 224.13 per 40 mg/2 mL pre-filled syringe, accessed 9 Sep 2026	One of the few HA products with a labelled peritendinous and intrasheath indication and a defined two-injection regimen, addressing a gap left by intra-articular products	No product-specific trial was retrieved; local reactions are labelled as very rare (<1 in 10,000) without a denominator; not for acute trauma	[145,159]
33	VISCOSEAL	n.a. (not FDA-approved)	n.a.	n.a.	Distinct post-arthroscopy indication as an irrigation-fluid replacement, at the lowest concentration in this table (0.5%)	Not a chronic osteoarthritis therapy and not comparable with viscosupplement courses; no product-specific trial retrieved	[146]
34	OSTENIL MINI	n.a. (not FDA-approved)	n.a.	n.a.	The only 1 mL small-joint presentation with an explicit label list of target joints, including facet and temporomandibular joints	Documentation is label-level only; small-joint efficacy must not be extrapolated from knee trials	[147]

Table 9: Musculoskeletal hyaluronic acid products: price by type and product-level appraisal (34 products).

All amounts in USD. [ASP] = Medicare average sales price payment limit per HCPCS billing unit from the file effective 1 July–30 September 2026, the quarter current at the 9 September 2026 evidence cut-off (a reimbursement limit, not a purchase price) [154]; [ASP-calc] = full-course cost calculated for this review as payment limit × labelled dose × injections; [DIST] = distributor list or sale price; [CASH] = consumer retail or discount-card price with the vendor's stated update date; [PATIENT] = patient-facing or manufacturer direct-pay price. The previously reported April–June 2026 limits [66] are superseded, and the file for 1 October–31 December 2026, published on 8 September 2026, is preliminary and future-

effective: it changes twelve of the thirteen codes — J7318 6.314/mg; J7320 4.231/mg; J7321 69.868/dose; J7322 17.940/mg; J7323 103.603/dose; J7324 116.793/dose; J7325 6.011/mg; J7326 524.063/dose; J7327 626.144/dose; J7328 0.550/0.1 mg; J7329 4.207/mg; J7331 3.115/mg (unchanged); J7332 10.188/mg [155]. Prices fluctuate continuously, are not comparable across types, and are not evidence of comparative clinical effectiveness. Distributor and retail pages are cited for price only, never for efficacy [76–83,105,159–161]. Prices converted from euro use the European Central Bank reference rate for 8 September 2026 (1 EUR = 1.1614 USD) [158].

Cross-cutting observations calculated for this review from the July–September 2026 file: calculated course costs span 186.90 to 870.29 (4.7-fold); per-milligram payment limits span 3.036 to 18.131 (6.0-fold); distributor list prices exceed calculated course costs by 3.7 times for one single-injection product and 7.9 times for another; manufacturer direct-pay at 97 per syringe undercuts every [CASH] and [DIST] price recorded here; and the two verifiable European retail prices (36.35 and 97.56 per syringe) sit below every United States figure of any type [87,154,159].

#	Product (applicant)	HA source	Concentration	Cross-linker and technology	Molecular-weight disclosure	Rheology (G'; tan δ; cohesivity; uptake)	Primary indication and plane	US premarket approval	Sources
1	Juvéderm Ultra XC (Allergan/AbbVie)	<i>Streptococcus</i> species	24 mg/mL	Cross-linked; 0.3% w/w lidocaine; cross-linker not named on the label	n.a.	207; 0.386; 96; 622	Mid-to-deep dermis for wrinkles and folds; lips and perioral area	P050047/S005 (7 Jan 2010); P050047/S044 (30 Sep 2015, lips)	[34,56,68]
2	Juvéderm Ultra Plus XC (Allergan)	<i>Streptococcus</i> species	24 mg/mL	Hylacross; 0.3% lidocaine	n.a.	263; 0.300; 112; 454	Mid-to-deep dermis, moderate–severe wrinkles and folds	P050047/S005 (7 Jan 2010)	[34,56,68]
3	Juvéderm Voluma XC (Allergan)	<i>Streptococcus</i> species	20 mg/mL	BDDE; Vycross; 0.3% w/w lidocaine	BDDE named; degree of cross-linking n.a.	398; 0.103; 40; 227	Deep subcutaneous and/or supraperiosteal: cheek, chin; supraperiosteal temple	P110033 (22 Oct 2013); S042 (2016, cannula); S047 (2020, chin); S070 (2023, temple)	[34,56,67]
4	Juvéderm Vollure XC (Allergan)	<i>Streptococcus</i> species	n.a. in US labelling (EU analogue 17.5 mg/mL)	Vycross; BDDE	n.a.	EU analogue 340; 0.135; 30; 184	Mid-to-deep dermis, moderate–severe wrinkles and folds	P110033/S020 (17 Mar 2017)	[34,56]
5	Juvéderm Volbella XC (Allergan)	<i>Streptococcus</i> species	15 mg/mL	Vycross; BDDE	n.a.	271; 0.144; 19; 133	Lips and perioral rhytids	P110033/S018 (31 May 2016)	[34,56]
6	Juvéderm Volux XC (Allergan)	<i>Streptococcus</i> species	25 mg/mL	Vycross; BDDE	n.a.	665; 0.074; 93; 253 — highest G' and lowest tan δ in this range	Subcutaneous and/or supraperiosteal jawline definition; infraorbital hollowing	P110033/S053 (2021); P110033/S065 (2022)	[34,56]
7	SkinVive by Juvéderm (Allergan)	<i>Streptococcus</i> species (platform)	n.a. (label not retrievable)	Vycross microdroplet platform	n.a.	n.a.	Intradermal injection to improve facial skin smoothness of the cheeks	P110033/S059 (11 May 2023)	[56]
8	Restylane / Restylane-L (Q-Med/Galderma; Medicis)	Non-animal, <i>Streptococcus</i> species (NASHA)	20 mg/mL	BDDE; NASHA; ±0.3% lidocaine	BDDE named	864; 0.214; 29; <100	Lip augmentation; submucosal implantation	P040024/S039 (2010); S051 (2011); S056 (2012)	[34,56,69]

9	Restylane Lyft with Lidocaine (Q-Med/Galderma)	HA generated by <i>Streptococcus</i> species	20 mg/mL	BDDE; stabilised in phosphate-buffered saline at pH 7; 0.3% lidocaine	BDDE named; degree n.a.	977; 0.203; 32; <100	Deep dermis to superficial subcutis; cheek; subcutaneous dorsal hand; chin	P040024/S073 (2015); S099 (2018, hand); S101 (2018, cannula)	[34,56,69]
10	Restylane Silk (Q-Med; Valeant/Medicis)	Non-animal <i>Streptococcus</i> (NASHA)	n.a.	BDDE; NASHA	n.a.	n.a.	Lip augmentation and dermal implantation for perioral rhytids	P040024/S072 (2014); S096 (2017, cannula)	[56]
11	Restylane Kysse (Q-Med/Galderma)	Bacterial origin	20 mg/mL sodium hyaluronate	BDDE (1,4-butanediol diglycidyl ether); lidocaine 3 mg/mL	BDDE named	236; 0.212; 85; 373	Submucosal lip augmentation; mid-dermis to subcutaneous for upper perioral rhytids	P140029/S021 (26 Mar 2020)	[34,56,70]
12	Restylane Defyne (Q-Med/Galderma)	Non-animal <i>Streptococcus</i>	20 mg/mL	BDDE; XpresHAn	n.a.	342; 0.137; 60; 318	Mid-to-deep dermis for deep folds; chin augmentation	P140029 (2016); S027 (2021, chin)	[34,56]
13	Restylane Refyne (Q-Med/Galderma)	Non-animal <i>Streptococcus</i>	20 mg/mL	BDDE; XpresHAn	n.a.	116; 0.431; 49; 516	Mid-to-deep dermis, moderate-severe wrinkles and folds	P140029 (9 Dec 2016)	[34,56]
14	Restylane Contour (Q-Med/Galderma)	Non-animal <i>Streptococcus</i>	n.a.	BDDE; XpresHAn	n.a.	n.a.	Cheek augmentation and midface contour deficiencies	P140029/S032 (28 Jun 2021)	[56]
15	Restylane Eyelight (Q-Med/Galderma)	Non-animal <i>Streptococcus</i>	n.a.	NASHA	n.a.	n.a.	Improvement of infraorbital hollowing	P040024/S135 (8 May 2023)	[56]
16	Restylane Skinboosters Vital / Vital Light (Galderma)	Stabilised HA of non-animal origin	Vital 20 mg/mL; Vital Light 12 mg/mL	Cross-linker n.a. on the label; lidocaine 3 mg/mL	Mean molecular weight n.a.; "stabilised"	Vital 667; 0.258; 27; <100. Vital Light 84; 0.583; 12; <100	Mid dermis; elasticity of lower cheek, jawline and upper neck; three treatments 2–4 weeks apart, maintenance every 4–6 months; maximum 3.5 mL per session and 17.5 mL per year	Not listed among FDA-approved dermal fillers; US status n.a. (fetched label is a European document)	[34,56,74]
17	Belotero Balance / Balance (+) ± Lidocaine (Merz)	Bacterially fermented from streptococcal cultures	22.5 mg/mL	BDDE; Cohesive Polydensified Matrix	BDDE named; degree n.a.	Balance+ 128; 0.641; 69; 664. Technology-level swelling 16.9 mL/g and cohesion 48 mg	Mid-to-deep dermis, moderate-severe wrinkles and folds such as nasolabial folds; infraorbital hollow	P090016 (2011); S028 (2019, lidocaine); S050 (2023, infraorbital)	[33,34,56,71]
18	Revanesse Versa / Versa+ (Prolenium)	n.a. on the label; contraindications reference streptococcal and Gram-positive bacterial proteins	25 mg/mL	"Bioresorbable cross-linked hyaluronic acid"; cross-linker not named	n.a.	n.a.	Mid-to-deep dermis for moderate-severe wrinkles and folds; intradermal use only	P160042/S001 (2017); S003 (2018, Versa+)	[56,72]
19	Revanesse Ultra / Lips+ (Prolenium)	As above	n.a.	As above	n.a.	n.a.	Ultra: mid-to-deep dermis. Lips+: submucosal lip augmentation	P160042 (2017, Ultra); S010 (2020, Lips+)	[56,72]

20	Teosyal RHA 2 / RHA 3 / RHA 4 (± Mepi) (Teoxane)	Non-animal origin	RHA 4: 23 mg/mL; RHA 2 and RHA 3: 23 mg/mL	BDDE, residual <1 ppm; degree of cross-linking <5% by nuclear magnetic resonance; lidocaine hydrochloride 0.3% by mass	Mean molecular weight >1 million Da — the only product here disclosing both molecular weight and degree of cross-linking	RHA2 319; 0.310; 77; 420. RHA3 264; 0.254; 109; 427. RHA4 346; 0.179; 115; 366	RHA 2/3 mid-to-deep dermis; RHA 4 deep dermis to superficial subcutis; RHA 4 must not be injected into epidermis, periorbital area, glabella or lips	P170002 (2017); S012 (2021); S026 (2023); S030 (2023)	[34,56,73]
21	Evolysse Smooth / Evolysse Form (Symatase)	n.a.	n.a.	n.a.	n.a.	n.a.	Dermal and subdermal injection for moderate–severe dynamic facial wrinkles and folds	P240022 (13 Feb 2025), the most recently approved HA filler in the FDA listing	[56]
22	Profililo / Profililo Body (IBSA Farmaceutici Italia)	n.a.	32 mg/mL total: 2 mL = 32 mg high-plus 32 mg low-molecular-weight HA (64 mg); Body 3 mL = 96 mg	Hybrid cooperative complexes (NAHYCO); no chemical cross-linker reported	High-molecular-weight 1,100–1,400 kDa; low-molecular-weight 80–100 kDa	n.a.	Skin laxity of face and neck, and body; bolus technique with 0.2 mL per point on face and neck and 0.3 mL per point on arms and abdomen; two sessions 30 days apart	Not listed among FDA-approved dermal fillers; US status n.a.	[46,47,56]
23	saypha MagIQ (Croma-Pharma GmbH, Austria)	<i>Streptococcus</i> species	23 mg/mL with 0.3% w/w lidocaine	BDDE, residual limited to 2 ppm	n.a.	n.a.	Mid and deep dermis for moderate–severe facial wrinkles and folds such as nasolabial folds, adults over 21; mean 1.54 mL per fold at initial treatment	P240008 (8 Sep 2025); CE mark May 2016, marketed in more than 70 countries and never withdrawn for safety or effectiveness	[125]
24	saypha ChiQ (Croma-Pharma GmbH)	<i>Streptococcus</i> species fermentation	23 mg/mL HA with 3 mg/mL lidocaine hydrochloride in phosphate-buffered saline	BDDE, residual limited to 2 ppm	n.a.	n.a.	Cheek augmentation and midface volume deficit by subcutaneous and/or supraperiosteal injection, adults over 21; median 4.0 mL for both cheeks	P250021 (12 Jun 2026); CE mark March 2016	[126]
25	Belotero Volume (+) Lidocaine (Merz North America)	Non-animal HA	26 mg/mL with 0.3% lidocaine	BDDE; Cohesive Polydensified Matrix volumising technology (CPM-HA-V)	n.a.	n.a.	Deep subcutaneous and/or supraperiosteal injection for midface volume deficit or contour deficiency, adults 22 years or older; trial volumes did not exceed 12 mL initially plus 6 mL at repeat treatment	P250020 (19 May 2026); registered in approximately 85 countries and never withdrawn	[127]

26	Belotero Intense (+) Lidocaine (Merz North America)	Non-animal HA with trace Gram-positive bacterial proteins	25.5 mg/mL with 3.0 mg/mL lidocaine	BDDE in physiological phosphate buffer	n.a.	n.a.	Submucosal and/or subcutaneous lip augmentation, adults over 21; supplied with two 27 G ½" needles	P250016 (9 Jul 2026); first approved in the European Union in October 2013 and registered in 78 countries outside the US	[128]
27	Teosyal RHA Redensity / RHA Redensity Mepi (Teoxane SA)	<i>Streptococcus equi</i> fermentation	15 mg/g with 0.3% lidocaine hydrochloride (Mepi variant: 0.3% mepivacaine)	BDDE; both cross-linked and non-cross-linked chains; described as the least cross-linked device of the resilient-HA range	n.a.	n.a.	Dermis and superficial dermis for moderate–severe dynamic perioral rhytids, adults 22 years or older	P170002/S012 (22 Dec 2021); mepivacaine variants launched in the US in late 2024	[129]
28	RHA Redensity Eye / RHA Redensity Eye Lido (Teoxane SA)	<i>Streptococcus equi</i> fermentation	15 mg/g; Eye Lido with 0.3% lidocaine hydrochloride, Eye with 0.3% mepivacaine hydrochloride	BDDE; physiological buffer at pH 7.3	n.a.	n.a.	Sub-dermis and suprapariosteum of the infraorbital region for moderate–severe tissue volume deficiency, adults 22 years or older; Eye supplied with a 25 G 1½" cannula	P170002/S050 (12 May 2026) — the first United States infraorbital indication on this platform	[130]
29	HARmonyCa / HARmonyCa Lidocaine (Allergan Aesthetics)	n.a.	20 mg/mL cross-linked sodium hyaluronate with calcium hydroxyapatite microspheres of 25–45 µm at 55.7% w/w, plus lidocaine	Cross-linked HA carrier with embedded calcium hydroxyapatite microspheres (hybrid); cross-linker not named	n.a.	n.a.	Facial soft-tissue augmentation in small homogeneous volumes into superficial fat compartments, deep subcutaneous or suprapariosteal planes; two 1.25 mL syringes per package	Not FDA-approved; US status not stated in the fetched sources	[117,118]
30	Neuramis Deep (Medytox, Korea)	n.a.	n.a. (not stated in the fetched trial)	BDDE; two-step "SHAPE" cross-linking with enhanced purification	n.a.	n.a.	Intradermal nasolabial-fold correction with a 27 G needle; recommended dose below 1 mL per side	Not FDA-approved	[113]
31	YVOIRE Classic / YVOIRE Y-Solution 720 (LG Chem, Korea)	n.a.	Classic 22 mg/mL; Y-Solution 720 20 mg/mL with 3 mg/mL lidocaine hydrochloride	BDDE; "high-concentration equalised" cross-linking (Classic) and stable high-concentration equalised (S-HICE) cross-linking with reduced BDDE (Y-Solution 720)	n.a.	n.a.	Classic: moderate–severe nasolabial folds, up to 1.5 mL per side with optional touch-up at 2 weeks. Y-Solution 720: midface volume deficiency, maximum 6.0 mL per midface	Not FDA-approved; Y-Solution 720 approved in the Republic of Korea in 2016	[114,115]
32	e.p.t.q. S300 (Jetema, Korea)	n.a.	n.a. (not stated in the fetched papers)	Cross-linked HA with lidocaine; agent not stated	n.a.	n.a.	Mid-face rejuvenation by injection into the upper antero-medial cheek in the pilot study	Not FDA-approved	[116]

33	Neauvia Organic Intense (Matex Lab SpA, Italy)	n.a.	28 mg/mL as listed by the distributor	Polyethylene glycol (PEG) cross-linker rather than BDDE; all gels of the range enriched with glycine and L-proline	n.a.	n.a.	Correction of moderate-to-severe nasolabial folds	Not FDA-approved; class III device under EU Regulation 2017/745	[119,150]
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Table 10: Aesthetic hyaluronic acid injectables and skin boosters: product characteristics (33 products).

Rows 23–33 were added in this revision: rows 23–28 are United States premarket approvals granted between December 2021 and July 2026, and rows 29–33 are products marketed outside the United States that carry product-specific human evidence. Rheology values are from a single dataset measured at 5 Hz and 0.8% strain and are reported as G' (Pa); $\tan \delta$; cohesivity (gmf); maximum water uptake (%); they are not interchangeable with values measured under other conditions. "n.a." indicates a field not verifiable from the cited sources. Brands are listed for product-literacy purposes only and are not endorsed.

#	Product	[DIST] per syringe (rows 1–22 effective 6 Dec 2021; rows 23–33 accessed 9 Sep 2026)	[PATIENT]	Strengths	Limitations	Sources
1	Juvéderm Ultra XC	270.00 (box of 2 × 1 mL = 540.00)	Brand average 775; 881 per syringe (211 prices, 45 clinics); HA filler national average 715	Longest US lip and nasolabial-fold dataset; 12-month lip responder rate 56.4%; mean about 9 months to repeat treatment	High water uptake (622%) can produce visible swelling; label reports very high short-term injection-site response rates	[68,89,90]
2	Juvéderm Ultra Plus XC	270.00 (box of 2 = 540.00)	Brand-level as above	Higher G' (263 Pa) than Ultra XC for deeper folds	Same swelling profile family; no separate durability dataset retrieved	[34,89,90]
3	Juvéderm Voluma XC	365.00 (box of 2 × 1 mL = 730.00)	Brand-level as above	Only product here with a 24-month cheek dataset (67.1% still improved) and a 13-month temple dataset (73.3% responders); three site-specific approvals	Device- or injection-related adverse events in 32.6% of the cheek study, rising with volumes above 9 mL and age above 60; supraperiosteal use is the setting of the bone-resorption signal	[56,67,89,90]
4	Juvéderm Vollure XC	329.50 (minimum 10 boxes; box of 2 = 659.00)	Brand-level as above	Mid-range G' for dynamic folds	Wholesale tier requires a 10-box minimum; US concentration not disclosed in the sources examined	[34,89,90]
5	Juvéderm Volbella XC	180.00 per 0.55 mL (box of 2 = 360.00); 329.50 per 1 mL (box of 2 = 659.00)	Brand-level as above	Lowest cohesivity (19 gmf) and low water uptake (133%) suit fine lip and perioral work	Belongs to the low-molecular-weight-containing family approved 2016–2020 reported to have the highest late-onset reaction incidence	[34,36,89,90]
6	Juvéderm Volux XC	n.a.	Brand-level as above	Highest G' (665 Pa) for jawline projection	High- G' product in a high-risk zone; delayed-onset nodules 0.33% across this product family in a 2,139-patient clinic series	[34,41,90]
7	SkinVive by Juvéderm	n.a.	National average 723; range 522–1,151; state averages 624 to 878	The only FDA-approved intradermal HA skin-quality product in the US (cheek smoothness)	Composition n.a.; indication limited to cheek smoothness; patient price varies 2.2-fold across states; the state table cites an unnamed source without a date	[56,90]
8	Restylane / Restylane-L	212.00 per 1 mL; 155.00 per 0.5 mL	Brand average 825; 818 per syringe (129 prices, 42 clinics)	Very high G' (864 Pa) with minimal water uptake, giving predictable non-swelling correction	Low cohesivity (29 gmf) and firm feel	[34,89,90]

9	Restylane Lyft with Lidocaine	226.00 per 1 mL	Brand-level as above	Only product here with an FDA-approved dorsal-hand indication; G' 977 Pa	24.7% of hand-study subjects had at least a 10-degree loss of thumb flexion persisting through 6 months; hand adverse events may last more than 96 days; effectiveness beyond 1 year not investigated	[34,69,89,90]
10	Restylane Silk	217.00 per 1 mL	800 per syringe (4 prices, 4 clinics)	Fine-particle lip and perioral product with cannula approval	Patient-price estimate rests on only four reported prices	[56,89,90]
11	Restylane Kysse	288.00 per 1 mL	Brand-level as above	Best-documented lip durability here (60% responders at week 48); treatment-related adverse events 21.1% with no treatment-related serious events; late-onset events 5.4% versus 5.7% control	97.8% reported some injection-site symptom, 3.4% disabling; strict volume caps (3 mL combined lips)	[70,89,90]
12	Restylane Defyne	275.00 per 1 mL	Brand-level as above	XpresHAn flexibility with a chin approval; G' 342 Pa, tan δ 0.137	Chin and jaw suprapariosteal placement is a bone-resorption signal site	[34,56,89,90]
13	Restylane Refyne	276.00 per 1 mL	Brand-level as above	Lowest-G' product in its range (116 Pa) for dynamic areas	High water uptake (516%) relative to other products of the same technology	[34,89,90]
14	Restylane Contour	303.00 per 1 mL	Brand-level as above	Dedicated cheek and midface approval (2021)	Rheology values n.a.	[56,89,90]
15	Restylane Eyelight	n.a.	n.a.	Dedicated infraorbital hollowing approval (2023), one of only two products with that indication	The infraorbital and periorbital region is a Grade 3 high-risk zone for vascular events	[35,56]
16	Restylane Skinboosters Vital / Vital Light	n.a.	n.a.	The only skin booster here with a quantified label protocol and annual volume cap (3.5 mL per session; 17.5 mL per year)	Not listed among FDA-approved fillers; cross-linker and molecular weight n.a.; no numerical duration of effect on the label	[56,74]
17	Belotero Balance (+)	189.00 per 1 mL	Brand average 700; 1,400 per syringe in a second aggregate resting on 8 prices from 5 clinics	Lowest wholesale price here; its technology shows the highest cohesion (48 mg) and swelling factor (16.9 mL/g) of those compared; mean 37-week interval between injections in extension	Label states that safety and effectiveness in the lips have not been evaluated and that use for contour defects other than nasolabial folds is not established, yet off-label periorbital use is widely marketed; the two patient-price sources differ two-fold	[33,71,89,90]
18	Revanesse Versa / Versa+	155.00 per 1.2 mL (box of 2 = 310.00)	478 per syringe (23 prices, 23 clinics)	Lowest per-mL wholesale cost; 25 mg/mL is the highest concentration among the US-approved products here	No maximum recommended volume on the label and syringe graduations described as not precise; cross-linker and HA source not named; extensive contraindication list including any anticoagulant or antiplatelet therapy	[72,89,90]
19	Revanesse Ultra / Lips+	155.00 per 1.2 mL (Lips+)	As above	Dedicated submucosal lip approval	Same labelling gaps as Versa	[56,72,89,90]
20	Teosyal RHA 2 / 3 / 4	International/import listings only: RHA1 219.00; RHA2 249.00; RHA3 249.00 (2 × 1.2 mL); RHA4 279.00; RHA Kiss with lidocaine 179.00	Collection average 825; 708 per syringe (25 prices, 11 clinics); Redensity 721 per syringe (6 prices, 6 clinics)	The most transparent product specification here: molecular weight >1 MDa, cross-linking <5% by nuclear magnetic resonance, residual BDDE <1 ppm, label-stated 15–18-month estimated lifetime and explicit numeric adverse-event frequency categories	Distributor pages do not state whether stock is US-authorised or imported, so authorised distribution status is n.a.; RHA 4 is prohibited in the periorbital area, glabella and lips while another product in the same family is approved for lips, so indication discipline must be product-by-product	[73,88,90]
21	Evolysse Smooth / Form	n.a.	n.a.	Newest FDA-approved HA filler (February 2025), indicated specifically for dynamic wrinkles	No independent clinical, rheological or price data retrievable	[56]

22	Profilo / Profilo Body	n.a.	n.a.	Largest post-marketing exposure dataset here: 1,091,956 estimated patients with 371 adverse events (0.034%), including 1 embolism and 1 vascular occlusion	Not listed among FDA-approved fillers; efficacy base of 9 studies and 278 participants, 8 single-centre, 6 with fewer than 30 participants, almost exclusively White women, manufacturer-funded with three employee co-authors; exposure denominator modelled rather than measured	[46,47,56]
23	saypha MagIQ	n.a. for the MagIQ presentation; the ex-US saypha Volume with lidocaine is listed at 69.00 per unit	National HA-filler average 715	Pivotal randomised blinded-evaluator trial met non-inferiority on the nasolabial-fold responder rate at week 24 (82.2% versus 81.9%; difference 0.37%, 95% CI -2.96 to 3.70; per-protocol 83.5% in both arms)	Injection-site reactions recorded in 243 of 255 patients (95.3%) after initial treatment; molecular weight and rheology not disclosed; the priced presentation is not the approved MagIQ stock-keeping unit	[90,125,160]
24	saypha ChiQ	n.a.	National HA-filler average 715	Adds a dedicated cheek and midface indication on the same platform, with a blinded-evaluator midface responder endpoint at week 24 and median 4.0 mL per treatment	Quantitative pivotal responder results were not extractable from the fetched approval summary, which documents design and safety collection only; rheology n.a.; no price identified	[90,126]
25	Belotero Volume (+) Lidocaine	349.00 per unit	Brand average 700	Randomised evaluator-blinded non-inferiority trial: midface volume-deficit scale improved -1.60 versus -1.5 for the comparator, with week-12 responder rates 95.8% (137/143) versus 95.7% (45/47); 82.7% of treatment-related events mild and no severe treatment-related events	Injection-site swelling 10.5%, pain 9.2%, haematoma 7.9%, induration 5.3%; volume cap of 12 mL initially; distributor listing may not be authorised United States stock	[90,127,160]
26	Belotero Intense (+) Lidocaine	109.50–219.00 (outlet price range)	Brand average 700	Lip indication approved on co-primary endpoints — a week-8 responder rate tested against a 50% threshold and non-inferiority in mean scale change (margin -0.5) — both required for success	Injection-site swelling, induration, pain, discoloration, bruising, erythema, oedema and oral herpes each at or below 5%; contraindicated with amide-anaesthetic hypersensitivity; wide outlet price range of uncertain provenance	[90,128,160]
27	Teosyal RHA Redensity / Redensity Mepi	219.00 (RHA1 presentation)	Redensity 721 per syringe (6 prices, 6 clinics)	Supported by a 52-week prospective randomised controlled trial in moderate-to-severe dynamic perioral rhytids; least cross-linked device of its range, matching a low-firmness indication	Distributor pages do not state whether stock is United States-authorized; perioral placement carries the highest injection-site-reaction burden of the range	[88,90,129]
28	RHA Redensity Eye / Eye Lido	n.a.	n.a.	First United States infraorbital approval on this platform (May 2026), supplied with a cannula for the Eye variant	The infraorbital and periorbital region is a Grade 3 high-risk zone for vascular events, and European use preceded United States approval without published comparative data	[35,130]
29	HAmonyCa / HAmonyCa Lidocaine	n.a.	n.a.	Prospective open-label post-marketing study: midface volume-deficit responder rate 82.8% at month 1 sustained to month 12, with investigator-rated global improvement in 98.5%; a 9-centre retrospective series of 162 participants reported no adverse events over at least 18 months and no ultrasonographic inflammation or granulomas in 64 participants	Open-label designs without a comparator; treatment-related injection-site pain 11.4%, injection-site mass 10.7% and headache 7.1%; "neocollagenesis" is a mechanistic assertion, not a measured human structural endpoint; the calcium hydroxyapatite component is not reversible with hyaluronidase	[117,118]

30	Neuramis Deep	59.00 for the Neuramis Volume with lidocaine presentation, tiered to 55.00 for 11–20 packs	n.a.	Phase III randomised, double-masked, matched-pairs, active-controlled trial against a stabilised comparator: wrinkle-severity change 1.63 ± 0.54 versus 1.44 ± 0.61 at 8 weeks ($p = 0.001$) and 0.50 ± 0.66 versus 0.34 ± 0.65 at 24 weeks	Local adverse events in 84.06% (58/69), bruising 69.57% and oedema 62.32%, although not significantly different from the comparator; concentration not stated in the trial; the priced presentation differs from the one trialled	[113,160,161]
31	YVOIRE Classic / Y-Solution 720	n.a.	n.a.	Randomised evidence in two markets: wrinkle-severity responder rates 81.03% at week 2 and 56.14% at week 26 for Classic, and a multicentre randomised evaluator-blind Chinese midface study of Y-Solution 720 with three-dimensional photographic volumetry	Responder rate roughly halves between week 2 and week 26; the midface trial used a no-treatment rather than active or sham control; no defensible price identified	[114,115]
32	e.p.t.q. S300	n.a.	n.a.	One- and two-year prospective blinded evaluation with three-dimensional imaging, plus a 2026 post-market follow-up study	Pilot sample of 11 subjects; adverse-event rates not stated; concentration undisclosed; no price identified	[116]
33	Neauvia Organic Intense	79.00 per 1 mL	n.a.	The only product tabulated here cross-linked with polyethylene glycol rather than BDDE, and enriched with glycine and L-proline — a chemistry that should be assessed on its own data	Evidence is a single post-market, open-label, single-centre study; PEG chemistry must not be pooled with BDDE products; concentration is distributor-stated rather than label-stated	[119,150,161]

Table 11: Aesthetic hyaluronic acid products: price by type and product-level appraisal (33 products).

All amounts in USD. For rows 1–22 the [DIST] figures are from the only itemised United States clinic wholesale sheet retrieved, with prices effective 6 December 2021 and therefore approximately five years old; for rows 23–33 they are non-US distributor listings accessed 9 September 2026, whose authorised-distribution status is not stated and which may not reflect United States supply. [PATIENT] prices are physician-reported, clinic-aggregated or patient-reported averages of differing vintage and sample size. Price types are not comparable with one another, fluctuate continuously, and are not evidence of comparative clinical effectiveness.

Market-level benchmarks, all [PATIENT] unless noted: physician-reported average 715 for HA fillers and 901 for non-HA fillers, with lip augmentation at 743; clinic-aggregated average 760.01 per syringe (871 prices from 125 clinics, low 500, high 950); patient-reported average 1,623 for all fillers, up to 5,500 for multiple areas, with state averages from 796 to 2,300; and [DIST] wholesale acquisition of 155.00–365.00 per syringe on a single United States clinic sheet effective 6 December 2021 [89,90]. Combining the last two figures gives product cost at roughly 22%–51% of the patient price for a single-syringe treatment — a calculation performed for this review across sources of different vintage, and an approximation rather than a margin measurement.

Regulation and quality

(Table 12) summarises the three jurisdictions. In the United States, intra-articular HA is a Class III device under 21 CFR 888.3027, product code MOZ, requiring premarket approval on the rationale that it temporarily replaces synovial fluid by physical viscoelastic action; in December 2018 the FDA published its intent to consider reclassifying these products as drugs, given evidence that effects may occur through

chemical or pharmacological action, and the outcome was not established by any source examined here [58,59]. Dermal fillers are likewise premarket-approved devices under active post-market signal management [56,61]. (**Table 14**) records developments to September 2026: four new premarket approvals and two panel-track supplements for fillers, against no original approval for an intra-articular HA product since March 2019 and no HA billing code outside the tabulated set [125–131,138,154,155]. An August 2025 advisory panel weighed a décolletage indication, breast-imaging interference and the bone-resorption signal [56]; the European Union approved a chin filler marketed on bone-mimicking rheology in August 2026 [140]; and the September 2026 United Kingdom tariff reimburses HA bladder instillations, tendon injections and eye preparations as appliances [156].

Jurisdiction and product type	Classification and legal basis	Key regulatory features	Unresolved items	Sources
United States, intra-articular HA	Class III medical device, 21 CFR 888.3027, product code MOZ, premarket approval; Orthopedic panel	Device rationale is temporary prosthetic replacement of synovial fluid providing physical viscoelastic lubrication; payer indication wording is uniform: treatment of pain due to knee osteoarthritis after failure of exercise and simple analgesics	In December 2018 the FDA stated its intent to consider classifying these products as drugs because effects may occur through chemical or pharmacological action; the outcome is n.a.	[57,58,59]
United States, dermal fillers	Class III-equivalent device implants approved by premarket approval; product codes LMH (face) and PKY (hand)	Approved for adults 22 years or older by category and site; FDA recommends against use in the glabella, nose, periorbital area, forehead, neck, breast, buttocks and feet, and against implantation into bone, tendon, ligament or muscle; needle-free injection devices are not approved; general-issues panel meetings held in 2021 and 2025	Device class is not stated on the FDA consumer page; MDR counts for blindness, infection, migration and death are n.a.	[56,60,61]
European Union, dermal fillers	Regulation (EU) 2017/745 Annex XVI Section 3, Group 3; common specifications in Commission Implementing Regulation (EU) 2022/2346, Annex IV. Annex VIII Rule 8: permanent fillers Class IIb, absorbable or biologically active fillers (all HA) Class III; Rule 14: lidocaine-containing fillers Class III	Scope covers prefilled means of introduction including syringes, hyaluron pens and dermarollers; documented risk management specific to the non-medical purpose; obligation to define excluded or specially managed user and consumer groups; information for safety not limited to labelling	Application dates of the common specifications n.a.; EU classification of intra-articular viscosupplements n.a.	[62,63]
European Union, biorevitalisation and mesotherapy	Excluded from Group 3 common specifications unless the intended purpose is or includes filling	Products marketed for biorevitalisation, dermal hydration, collagen synthesis, fibroblast stimulation or skin radiance fall outside the filler common specifications precisely because they do not fill	Regulatory route for such products when not intended for filling is not specified in the fetched guidance	[63]
Brazil, injectable fillers (ANVISA)	Medical devices of risk class III or IV; marketing permitted only with ANVISA registration	March 2026 recommendation to use fillers only within approved indications; listed risks include pulmonary embolism, temporary and permanent visual impairment from vascular occlusion, granulomatous inflammation and renal complications; practitioners must verify registration, service authorisation and professional qualification, explain immediate, early and late complications and provide a traceability card; compounding pharmacies may not prepare intradermal fillers	Named approved anatomical regions, permitted volumes and resolution numbers n.a.; ANVISA position on intra-articular HA n.a.	[64,65]

Table 12: Regulatory framework for hyaluronic acid products by jurisdiction.

Development	Date	Detail as stated in the source	Why it matters	Sources
Four new United States premarket approvals of HA fillers	8 Sep 2025 – 9 Jul 2026	saypha MagIQ (P240008, 8 Sep 2025); Belotero Volume (+) Lidocaine (P250020, 19 May 2026); saypha ChiQ (P250021, 12 Jun 2026); Belotero Intense (+) Lidocaine (P250016, 9 Jul 2026)	Two new applicants and two platform extensions, each with pivotal randomised active-controlled data and quantified injection-site reaction rates (Tables 10 and 11)	[125–128]
Two panel-track supplements on the resilient-HA platform	18 Sep 2025 and 12 May 2026	RHA 4 mepivacaine formulation renamed RHA Dynamic Volume (P170002/S048); RHA Redensity Eye and Eye Lido approved for the infraorbital region (P170002/S050)	The first United States infraorbital indication on this platform, in a Grade 3 high-risk zone; the rename is an alias, not a new molecule	[130,131]

No new intra-articular HA approval	—	No original United States premarket approval for an intra-articular HA product after Triluron (26 March 2019); no HA billing code outside the thirteen existing J-codes in either the July–September or the October–December 2026 Medicare payment-limit file	The aesthetic pipeline is active while the musculoskeletal one is static, so "new HA" in orthopaedic marketing generally means a new brand of an existing class	[138,154,155]
FDA General Issues Panel on dermal fillers	13 Aug 2025	Panel considered a proposed décolletage indication, filler interference with breast imaging and screening, premarket and post-market assessment and filler removal; the executive summary reports 17,768 all-time serious-injury device reports (1,478 in 2023; 1,179 in 2024 to November), abscess 1,235, nodules 1,038, obstruction or occlusion 986, granulomas 846, three reports of bone resorption after supraperiosteal injection, and HA fillers in 77 of 186 (41.4%) unapproved upper-body-site reports against 5,331,426 HA filler procedures in 2023	Establishes the current United States surveillance picture and identifies bone resorption as a newly recognised event; incidence still cannot be derived from report counts	[56]
Septrafil recall	15 Mar 2024	Recall record states that product "was distributed in the United States without proper regulatory approval"	Regulatory compliance, not device failure, is a live risk even for long-established HA products	[139]
European Union approval of a bone-mimicking chin filler	11 Aug 2026	Restylane Shaye approved under the Medical Device Regulation for temporary chin augmentation, with approvals spanning Europe, Canada and Brazil	Marketing now advances rheological "bone mimicry" as a differentiator; the claim is mechanical, not regenerative, and the product is not FDA-approved	[140]
Cartilage-repair pipeline	31 Oct 2025	Third and final premarket-approval module for the Hyalofast scaffold filed after mixed phase III (FastTRACK) results; more than 35,000 patients treated in more than 35 countries since 2009	The most advanced HA cartilage-repair programme still has no randomised success on its co-primary endpoints, so Tier 4 remains unestablished	[55,149]
New United States clearance in gynaecology	1 Apr 2026	Hyaluronic acid vaginal suppositories 5 mg and 10 mg cleared by premarket notification (K260007)	Device-route expansion in an indication where the comparative evidence remains a single small randomised pilot	[137]
Quarterly movement of Medicare payment limits	1 Jul 2026 and 1 Oct 2026	The file effective 1 July 2026 was current at the cut-off; the file for 1 October–31 December 2026 was published on 8 September 2026 as preliminary and changes twelve of thirteen HA codes	Any published HA price must state its file, quarter and type; comparisons across quarters are not like-for-like	[154,155]
United Kingdom reimbursement listing	Sep 2026	Drug Tariff Part IX lists HA bladder instillations, two HA injection appliances, roughly 50 HA eye-drop presentations, two HA eye ointments and HA vaginal and topical preparations with basic prices	Provides official non-US price anchors for indications with no United States reimbursement pathway	[156]

Table 14: Hyaluronic acid regulatory, safety and reimbursement developments to 9 September 2026. Dates are decision or publication dates as stated in the cited source. Regulatory approval is not evidence of comparative effectiveness.

In the European Union, resorbable dermal fillers are Annex XVI Group 3 products under Regulation (EU) 2017/745 with common specifications in Implementing Regulation (EU) 2022/2346, and all HA fillers are Class III [62,63]. Mesotherapy products marketed for biorevitalisation are excluded from those common specifications because they are not used for filling [63], and the European classification of intra-articular viscosupplements is not addressed by that guidance.

In Brazil, ANVISA regulates injectable fillers as risk class III or IV devices marketable only with registration, and in March 2026 recommended use only within approved indications, warned that non-indicated regions or volumes may cause incapacitating or difficult-to-manage harm, and required delivery of a product traceability card [64]. Named approved regions, permitted volumes and any ANVISA position on intra-articular HA were not obtainable.

Discussion

The direction of effect for intra-articular HA is consistent — a small benefit over placebo — but the magnitude spans from clinically irrelevant to large, and methodology rather than newly discovered

biology explains that span. Methodological heterogeneity is extreme, reaching 75%–78% in the largest analysis and precluding pooling altogether in one review of injection regimens [9,13]. Publication bias and small-study effects are evidenced by funnel asymmetry, positive Egger's tests and the collapse of the pooled effect from -0.37 to -0.03 among unpublished trials [9,10]. Product non-equivalence means that "HA versus placebo" averages across products differing in origin, molecular weight, cross-linking, concentration, dose and regimen, while regulators have granted equivalence across an origin difference linked to a four-fold difference in flare-up rates [12,18,32]. Industry sponsorship and authorship overlap appear on both sides of the guideline dispute and are structural in the aesthetic literature [24,31,46,47]. Class-wide extrapolation is therefore unjustified: neither a favourable trial of an ultra-high-molecular-weight single injection nor a null trial of a low-molecular-weight five-injection course licenses a conclusion about "hyaluronic acid".

The second theme is the regeneration gap. Tier-1 evidence that HA sustains the progenitor niche and functions as a tunable scaffold is robust [7,8]; Tier-2 evidence supports modest, product-dependent symptomatic knee benefit below the minimal clinically important difference [9,22]; Tier-3 evidence supports volumisation with defined durations and, far more weakly, skin-quality improvement [45,67,70]; and Tier-4 evidence is not established for any product examined here — the scaffold with the most convincing histology had no control arm, the one with a randomised control failed its co-primary endpoints, and the most widely marketed cartilage scaffold has only non-randomised comparative data with a pivotal trial reported as mixed [54,55,149]. Marketing language migrates upward across these tiers and regulation does not restrain it: the preparations most insistently called regenerative are precisely that European guidance excludes from filler common specifications because they do not fill [63].

Safety and price require the same discipline as efficacy. Serious adverse events were increased in both large knee analyses, ultra-high-molecular-weight product carried a 37.5% local adverse-effect rate in the hip, and the aesthetic burden is real even though surveillance data cannot yield incidence [9,10,27,56]. Acquisition cost, reimbursement limit and patient price are routinely conflated commercially [89,90,154], yet neither price nor coverage status is evidence of effectiveness — as the guideline authors' explicit decoupling of their recommendation from coverage decisions illustrates [20].

Limitations

The limitations follow from the design. Evidence identification was structured but not systematic: because exact strings and per-source yields were not preserved, the search is neither exhaustive nor formally reproducible and studies may have been missed. Screening and selection were performed by a single author without duplicate independent screening; no selection flow is reportable, no protocol was registered, and no PRISMA-based process is claimed. No risk-of-bias instrument or de-novo certainty grading was applied, so every certainty statement inherits the strengths and weaknesses of its source, several of which reported none (**Table 7**). Only English-language full texts were synthesised, risking language bias. Product and price data came from labelling, payer policies, pricing files and vendor pages of differing vintage — including one wholesale sheet effective December 2021 — and several fields remain "n.a."; coverage is broad but not exhaustive, specifications for products marketed outside the United States derive from labels and regulatory summaries rather than independent measurement, and euro or

sterling conversions rest on a single day's reference rate. Finally, overlapping primary trials across the included reviews were not quantified, so agreement between reviews should not be read as independent replication.

Domain	Synthesis size	Certainty as reported by the source	Source
Knee osteoarthritis versus placebo (pain, function, serious, gastrointestinal and local adverse events)	169 trials, 21,163 participants	Low (GRADE) for all five outcomes	[9]
Knee osteoarthritis, guideline recommendation	AAOS systematic review	Moderate strength, downgraded one level	[22]
Knee osteoarthritis, low-risk-of-bias subset	8 trials, 2,199 participants	Not reported	[11]
Knee osteoarthritis, guideline-anchoring analysis	89 trials, 12,667 adults	Not reported	[10]
Hip osteoarthritis	7 trials, 982 patients	Not reported (Level I designation only)	[25]
Hip osteoarthritis, high-molecular-weight HA	4 studies	Not reported; all outcomes non-significant	[26]
Shoulder osteoarthritis	15 studies, 1,023 subjects	Not reported; mean PEDro 7.2; 46.7% with probable randomisation bias	[28]
Ankle osteoarthritis	Safety data only	Pooled efficacy not available	[29]
Injection-regimen comparisons	11 studies	Meta-analysis not possible for heterogeneity	[13]
Corticosteroid versus HA versus platelet-rich plasma versus combination	35 studies, 3,104 participants	Certainty, I ² and inconsistency all not reported	[14]
Chronic wounds	12 trials, 1,108 participants	Very low for every reported outcome	[48]
Dry eye	18 studies; 10 trials meta-analysed	Not reported	[50]
Filler adverse events and their treatment	182 studies	Very low; most studies small and non-comparative	[39]
Filler blindness prevention consensus	Expert consensus	Level of Evidence 5	[35]
Skin boosters	Narrative review	Limited by heterogeneity and absent standardised protocols; no pooled estimate	[45]
Hybrid cooperative complexes	9 studies, 278 participants	8 of 9 single-centre; 6 of 9 under 30 participants; manufacturer-funded with employee co-authors	[46]
HA scaffold plus marrow concentrate	Pivotal randomised trial	Co-primary endpoints not met; positive findings post-hoc	[55]
HA hydrogel plus cord-blood mesenchymal stromal cells	Phase I/II, 7 patients	Uncontrolled, single-arm, single-centre	[54]

Table 7: Evidence certainty by domain, as stated by the source syntheses.

Clinical decision framework

The framework in (Table 13) translates the evidence tiers into practice decisions. Its logic is that recommendation strength should track comparator-controlled evidence for the specific product and site in use, that product identity must be documented rather than assumed interchangeable, and that consent should present both the probability and the prognosis of the relevant complication. Nothing in it substitutes for the applicable label.

Decision point	Framework position	Evidentiary basis
Knee osteoarthritis, first-line	Do not offer intra-articular HA as first-line therapy; exercise, weight management and simple analgesia precede it	AAOS states HA is not recommended for routine use, with the recommendation clarified as pertaining to first-line treatment [22,23]

Knee osteoarthritis, selected patients	Consider a single-course trial in patients with persistent symptoms who have failed or cannot take other options, provided the expected benefit is described as modest, product-specific and on average below the minimal clinically important difference, and provided a responder threshold and reassessment date are set in advance	Pooled effect below MCID at low certainty [9]; larger effects only in low-risk-of-bias subsets [11]; 86% of organisations neutral or in favour [24]
Product selection for the knee	Prefer bacterial-fermentation origin and, where a class choice exists, higher-molecular-weight or stabilised single-injection products; record brand, origin, molecular weight, cross-linking, concentration, total dose and injection number in the notes	Bio-fermentation HA had fewer effusions and a 3.04% versus 13.19% acute flare-up rate; $\geq 3,000$ kDa products more favourable; single injections not inferior to multi-injection courses [12,13,32]
Regimen	Do not escalate injection number to seek efficacy; five-injection courses are not superior to three	No consistent difference between single- and multi-injection regimens [13]
Hip, shoulder, ankle, thumb base	Treat as off-guideline or evidence-limited; the hip carries a strong recommendation against and the highest reported local adverse-effect rate for ultra-high-molecular-weight product	ACR strong recommendation against for hip; ultra-high-molecular-weight local adverse effects 37.5% [20,27]
Platelet-rich plasma versus HA	Present platelet-rich plasma as probably superior on 9–12-month function but with fragile pooled significance, non-standardised preparations and a strong guideline recommendation against; do not present combination therapy as established	Odds ratio 2.19 with a fragility index of about nine events; ranking-only network analysis; ACR recommendation against platelet-rich plasma [14,15,20]
Cartilage repair with scaffolds and cells	Offer only within trials or registries; describe as investigational	Uncontrolled 7-patient series; pivotal trial failed both co-primary endpoints [54,55]
Aesthetic product-to-plane matching	Match rheology to plane and indication, not brand to fashion: low-G', low-cohesivity, low-swelling gels superficially and in dynamic areas; high-G', high-cohesivity gels for suprapariosteal projection	Product-level G' 40–1,055 Pa, $\tan \delta$ 1.050–0.074, uptake <100%–700% in one internally consistent dataset [33,34]
Aesthetic volume and site discipline	Respect label volume caps and approved sites; recognise glabella, nose, periorbital region, forehead and neck as sites the FDA recommends against, and document off-label use and consent explicitly	FDA unapproved-site list; ANVISA March 2026 recommendation; 186 serious-injury reports from unapproved upper-body sites [56,60,64]
Skin boosters	Offer for skin quality and hydration, not volume; state that neocollagenesis evidence is small-scale and that durable regeneration is unproven; prefer products with a defined label protocol and volume cap	Intradermal versus subdermal difference; observational evidence base; single product with label-defined protocol and annual cap [42,44,45,74]
Consent for filler injection	Disclose both the low probability and the poor prognosis of visual compromise, the possibility of delayed-onset nodules peaking at 3–4 months, and the availability but incomplete efficacy of hyaluronidase	Blindness at or below 1 per 100,000 syringes; visual compromise 1–2 per 1,000,000 with 19% improvement; late-onset reactions 0.33%–4% [35,36,39,40,41]
Pre-procedure screening	Delay for recent dental or barrier-compromising procedures, active infection, active inflammation or active autoimmune or granulomatous disease; identify lidocaine, Gram-positive protein and bee or wasp venom allergy before injection	Late-onset reaction consensus prevention recommendations; hyaluronidase allergy risk after venom anaphylaxis [36,38]
Suspected vascular occlusion	Treat immediately: hyaluronidase 1,500 units reconstituted in 1 mL of bacteriostatic saline or lidocaine, infiltrated into the affected artery and the surrounding ischaemic territory, with reassessment and re-dosing approximately every 15–20 minutes while capillary refill exceeds 3 seconds; high-dose pulsed protocols total 450–1,500 units over up to four cycles; give within 4 hours where possible	Emergency protocols and dose ranges as published; retinal circulation must be restored within 60–90 minutes [37,38]
Elective dissolution	Treat to effect rather than to a fixed dose, avoid concentrations below 1,500 units in 5 mL, reassess at 48 hours, and defer re-injection of filler for at least 2 weeks	Hyaluronidase guideline; native HA restored within 15–20 hours [38]
Traceability and documentation	Record product, lot, volume, site and plane for every injection, and provide the patient with product information where required by the applicable regulator	ANVISA requires delivery of a product traceability card with a copy in the record [64]
Cost discussion	Quote acquisition cost, reimbursement limit and patient price separately, and state that price does not indicate effectiveness	Payment limits, wholesale sheets and patient-price aggregates differ several-fold and by type [66,89,90,154]

Table 13: Clinical decision framework for hyaluronic acid, by evidence tier.

Conclusion

HA is simultaneously one of the best-characterised molecules in matrix biology and one of the most over-interpreted in clinical practice. It is a versatile, biocompatible, tunable scaffold for cell and drug delivery; intra-articular formulations give modest, product-dependent symptomatic relief that on average does not reach the minimal clinically important difference and carries a small excess of adverse events; aesthetic formulations reliably restore volume for defined, product-specific durations, with a small but non-trivial burden of vascular and delayed inflammatory complications mitigated by genuine reversibility; its ophthalmic, adhesion-barrier and bulking uses are valuable precisely because they are mechanical; and claims of regeneration, biostimulation and restored skin quality rest mainly on small, heterogeneous, frequently industry-linked studies. Progress requires product-level reporting, responder analyses anchored to the minimal clinically important difference, resolution of the device-versus-drug question, standardised rheology assays, independent skin-quality evidence, and separation of acquisition from patient price.

Declarations

Ethics approval and consent to participate: Not applicable. This manuscript is a review of published literature, regulatory documents and publicly available product and pricing information; it does not involve new human participants, animals or identifiable patient data.

Consent for publication: Not applicable.

Availability of data and materials: All data discussed are contained within the manuscript and its tables, and derive from the publicly accessible sources listed in the references; no new datasets were generated or analysed.

Supplementary material: A supplementary appendix, Global Register of Commercial and Clinically Used Hyaluronic Acid Products, accompanies this article. It lists 149 named products, product families and presentations across fifteen application categories — intra-articular and tendon products, aesthetic fillers and skin boosters, ophthalmic viscosurgical devices and tear substitutes, wound care, urology, gynaecology, bulking agents, adhesion barriers, ear-nose-and-throat, dental and cartilage-repair products — with concentration, molecular weight, architecture, labelled indication, strongest product-specific human evidence, adverse effects, verified price by type and evidence-integrity class, each cell hyperlinked to the primary document that states the value. The appendix records no product meeting the criterion of demonstrated regeneration, and its price and evidence conventions match those used here.

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