

Hyaluronic Acid / Viscosupplementation (Re-Review)

Topic & Final Key Questions - Public Comment

May 14, 2013

Health Technology Assessment Program (HTA)

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Hyaluronic Acid/Viscosupplementation

**Response to Topic and
Public Comments on Key Questions**

May 14, 2013

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Topic and Key Questions - Public Comment

Hyaluronic Acid/Viscosupplementation

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document.

Draft key questions for each WA HTA report are posted online in order to gather public input and any additional evidence to be considered in the evidence review. Since key questions guide the evidence report, WA HTA seeks input on whether the questions are appropriate to address its mandate to gather evidence on safety, efficacy, and cost-effectiveness relevant to coverage determinations. Input about the following is especially helpful:

- Are appropriate populations or indications identified?
- Are appropriate comparators identified?
- Are appropriate patient-oriented outcome measures included?
- Are there special policy or clinical considerations that could affect the review?

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cited evidence, the vendor was encouraged to consider inclusion of this evidence in the report.

This document responds to comments from the following parties:

- Samir Bhattacharyya, PhD, Suresh Aravind, MD, MBA, Brad Bisson, MPH, Brooks Story, PhD; DePuy Mitek, Inc.
- Anke Fierlinger, MD, Medical Director, Orthopaedics, Medical Affairs, Ferring Pharmaceuticals, Inc.
- Peter Heeckt, MD, PhD; Chief Medical Officer, Bioventus
- Biji Joseph, PharmD, MBA, Director, Medical Affairs, Sanofi Biosurgery
- Robert M. Liddell, MD, Center for Diagnostic Imaging (CDI), National Section Leader—MSK subspecialty (representing CDI-Puget Sound and the 15 subspecialized interventional radiologists who partner with CDI in the Puget Sound region)
- Louis F. McIntyre, MD, President, Advocacy for Improvement in Mobility
- Eric Rugo, Stryker Orthopaedics
- Steven St. George, Manager, Market Access and US reimbursement, Zimmer, Inc.

Table 1 provides a summary of comments with responses.

Table 1. Public Comment on Topic and Key Questions for Hyaluronic Acid / Viscosupplementation

Key: HA, hyaluronic acid or hyaluronan; IA, intra-articular; MCID, minimal clinically important difference; NSAID, nonsteroidal anti-inflammatory agent; OA, osteoarthritis; PICO, populations-interventions-comparators-outcomes; QALY, quality-adjusted life-year; QOL, quality of life; TKA, total knee arthroplasty; VS. Viscosupplementation

Comments on Topic	
Comment and Source	Response
December 3, 2012 Letter from Samir Bhattacharyya, Suresh Aravind, Brad Bisson, and Brooks Story; DePuy Mitek, Inc.	
<p>“We strongly believe that the clinical evidence continues to support the listing of viscosupplementation with hyaluronic acid (HA) as a covered benefit for the treatment of pain associated with osteoarthritis (OA) of the knee, as initially supported through the Washington State HTA coverage policy of 2010.” The commenters note the need for clinicians to have multiple options to offer patients according to “needs, co-morbidities, and response to therapy” and describe the limitations of NSAIDs, intraarticular injection of corticosteroids, and joint replacement surgery.</p>	<p>Thank you for your comments. No change to topic. Response to more specific comments follow.</p>
<p>The commenter cites and describes conclusions from systematic reviews included in the 2010 report plus a new systematic review by Bannuru et al. (2011), refers to the definition of minimal clinically meaningful improvement as defined by the IMMPACT group, and suggests that the different conclusions reached in various systematic reviews were due to differences in methodology.</p>	<p>The new review by Bannuru et al. will be included in the updated report. IMMPACT recommendations will be taken into account if they are still current.</p>
<p>“A recent analysis by Rutjes et al (August 7th, 2012) on the treatment of osteoarthritis with viscosupplements however, comes to very different conclusions than the four prior systematic reviews. One should expect from the authors' summary that there was a lack of efficacy analyses across all 71 studies and that they would have provided evidence, showing this deficiency. What the authors’ presented was, out of 69 studies with reported effect sizes, 60 (87%) showed an effect < 0 (favoring HA), and 49 (71%) showed an effect size < -0.176</p>	<p>Thank you for your analysis. These comments will be considered in the review of the meta-analysis by Rutjes et al.</p>

Comments on Topic	
Comment and Source	Response
<p>(equivalent to a difference of 0.44 cm, with an assumed SD of 2.5 cm). In addition, the authors used a clinically importance difference between the treated group and the control groups of 0.9 cm on a 10 cm scale to assesses the efficacy of viscosupplementation. This cutoff is inappropriate given the difference between placebo and various proven first and second line treatments for osteoarthritis ranged from 0.44 cm to 0.65 cm. These values represent the incremental and meaningful benefit of a therapy after subtracting the placebo and other non-specific effects.”</p>	
<p>“From the safety standpoint, the Serious Adverse Events (SAEs) listed as concerns involve disparate body systems, unique pathophysiologies and appear unrelated to each other mechanistically. . . it is unclear how intra-articular injections of HAs can be causally related to such a diverse set of SAEs (such as cancer, GI, Cardiovascular) linked to different body systems. While an increase in reported adverse events is statistically apparent, in the absence of a plausible biological mechanism that could generate these events, some form of biased ascertainment in reporting cannot be ruled out. Moreover, communication with Dr. Baraf (a study author in Supplement 14 SAE review which contributed 4 of the 6 cancer cases referenced in the Rutjes meta-analysis), indicate that of the 4 subjects with cancers (breast, prostate, squamous and melanoma) discovered within just 16-74 days post treatment, none were judged by investigators to be related to study treatment. Post marketing safety surveillance data from over 5 million injections of ORTHOVISC® worldwide in patients with osteoarthritis has shown no signals or trends suggestive of such treatment related serious adverse events. We believe that this meta-analysis evidence citing concerns over safety and efficacy from the use of viscosupplements, does not address the causality or mechanisms of the SAEs, does not reflect the findings from other Level 1 meta-analyses, and has methodological challenges that could affect the conclusions and current treatment paradigm.”</p>	<p>Thank you for your analysis. These comments will be considered in the review of the meta-analysis by Rutjes et al.</p>

Comments on Topic	
Comment and Source	Response
Letter from Anke Fierlinger, Ferring	
<p>“We maintain that viscosupplementation with hyaluronan (HA) is an effective and safe option for patients not achieving adequate pain relief with other interventions or who cannot tolerate adverse events (AEs) associated with acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) or intra-articular (IA) corticosteroid injections, or are unwilling to accept the well-known risks associated with these drugs.”</p>	<p>Thank you for your comments. The cited references will be considered for inclusion. No change to Topic. Responses to more specific comments follow.</p>
<p>“Our concern is that the recommendation for coverage of viscosupplementation will rely on the review of the meta-analysis published by Rutjes et al in Ann Intern Med, Aug 2012.” The commenter’s critique of the meta-analysis included the following points:</p> <ul style="list-style-type: none"> • General low trial quality, as acknowledged by the authors • Strong conclusion regarding safety even though safety data were often not reported • No accounting for randomized versus quasi-randomized studies; use of saline injection, sham treatment, or no intervention as the control; different measurement times for calculation of effect size • Unclear calculation of effect size and results that conflict with some of the data reported for individual trials • No reporting of safety data for control groups • Pooled data for products of different molecular weights and structure 	<p>These comments will be considered when analyzing the results reported by Rutjes et al.</p>
<p>The commenter cites 8 randomized controlled trials (RCTs) with sample sizes ≥ 200 that have been published since the last report and states “results are consistent with the most recent meta-analysis for IA HA.</p>	<p>The 8 cited trials and the referenced meta-analysis by Bannura et al. (2011) will be covered in the report.</p>

Comments on Topic	
Comment and Source	Response
<p>“Demonstration of a significant benefit with active treatment versus IA saline in patients with knee OA is often complicated by the fact that this ‘control’ typically produces significant improvements from baseline in patients with this condition.”</p>	<p>The cited references will be considered for the report.</p>
<p>“The Hayes 2010 report stated that adverse events (AEs) increase with repeat courses of IA HA.¹⁹ This may be true for some, but certainly not for all HA preparations. The 26-week extension of FLEXX Trial showed no significant increase in AEs and no joint effusions among patients who received a second course of 3 weekly injections IA HA.^{13,25} Results from the AMELIA trial also indicated no significant increase in AEs with repeated series of IA HA injections over 40 months.¹⁶”</p>	<p>The extension of the FLEXX Trial will be included in the report.</p>
<p>“It has been demonstrated that administration of IA HA can delay TKR in patients with advanced OA who were candidates for this procedure in a retrospective review of patient records in a single orthopedic specialty practice.”</p>	<p>The cited study (described in a review by Waddell et al. [2007]) was omitted from the previous report because it was a case series and thus does not demonstrate a causal relationship between use of IA HA and delayed TKR.</p>
<p>“A single treatment course of IA HA (1–5 injections depending on the HA preparation) typically provides 3–6 months of analgesia.³² IA HA is well tolerated and the most common AE is mild, short-lived injection-site pain and inflammation. There are currently there are no treatments that provide equivalent, prolonged pain relief similar to IA HA. Based on evidence supporting safety, efficacy, and cost-effectiveness of HA/viscosupplementation, we request that the Health Technology Clinical Committee considers to retain a covered benefit for treatment of pain associated with knee OA.”</p>	<p>The cited reference is a VA Clinical Guidance; its recommendations were reported in the 2010 report and will be included in the new report if they are still current.</p>

Comments on Topic	
Comment and Source	Response
December 3, 2012 Letter from Biji Joseph, Sanofi Biosurgery	
<p>“We believe that a re-review is unwarranted based solely on the strength of the data in the Rutjes publication for the following reasons:”</p>	<p>Thank you for your comments.</p>
<p>“A fair amount of data analyzed in the Rutjes et al meta-analysis for the class came from products not approved for use in the U.S.”</p>	<p>These various critiques of the review by Rutjes et al. will be considered in the updated report. The new review by Bannuru et al. (2011) will also be included.</p> <p>No change to topic.</p>
<p>“To their credit, Rutjes et al included un-published data in the meta-analysis. However, it is unclear if the unpublished data included would have met standards for publication in peer-reviewed journals.”</p>	
<p>“Despite inclusion of a few unpublished trials, which may have resulted in a diminution in the calculated effect size of the class, the overall analysis (figure 1 in the article) illustrated that VS had a moderate ES, which met their prespecified minimal clinically important difference of - 0.37.1 Despite meeting a raised threshold for clinically relevant ES, their conclusions regarding efficacy and recommendation for VS use are not supported by their own findings. Their conclusions/recommendations have been wrapped in an unjustifiably negative interpretation in the discussion section.”</p>	
<p>“The researchers have not indicated how different pain scales (VAS, Likert, categorical scales etc) were converted for pooling let alone how many scales had to be converted. They did NOT use the same variable consistently when pooling the outcome data. They used whichever variable the study in question had that was highest on the OMERACT-OARSI OA study hierarchy. Nick Bellamy had argued that this might not be appropriate for pooling.² This is a major methodological weakness of the study which renders their findings less than rigorous for clinical decision making.</p> <p>Other researchers such as Wang et al got around different scales and time points by using all the data, calculating SPID, and NORMALIZING IT TO PERCENT CHANGE.”</p>	

Comments on Topic	
Comment and Source	Response
<p>“The trial data reviewed by the US Food and Drug Administration (U.S. FDA) for Synvisc-One (hylan G-F 20) marketing registration had an ES of -0.23.4 Rutjes et al have raised the expectation on ES to an even higher level (-0.37) and lowered the ES of the Synvisc-One registration trial to -0.11 in their analysis.1 Moreover, they derived clinical relevance based on artificial back transformations from ES to mm on VAS scale. Their method of translating ES to a pain scale (-0.37 = 9mm on VAS) has not been validated to our knowledge. A published consensus statement from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, or IMMPACT group, urged considering improvements WITHIN treatment groups or patients in chronic pain trials. In addition to ES, which is statistical in nature, IMMPACT considered pain reductions of 30% or more to be moderately clinically important.5 Mean pain was reduced 36% over 26 weeks in patients treated with Synvisc-One.”</p>	
<p>“ES of <0.4 are considered to be clinically meaningful. The mainstays of pharmacologic treatment of OA are acetaminophen and oral NSAIDs. Acetaminophen is recommended in all major guidelines for Knee OA pain, yet its effect size is <0.20. The recent OARSI expert consensus Guidelines for the treatment of OA of the knee and hip noted the following effect size.” [acetaminophen, 0.10; NSAID class, 0.29; topical NSAIDs, 0.44; IA hyaluronic acid, 0.22]</p>	
<p>“The role and importance of patient education in the management of pain due to OA had been studied in two meta-analyses, but the ES for pain relief was considered small (0.06 95% CI 0.02, 0.10).7 Nevertheless, patient education is recommended universally in all major OA guidelines as the foundation of non-pharmacological treatment.”</p>	
<p>“The duration of efficacy does not exceed 6 months with one course of treatment for all VS products approved by the U.S. FDA.8-14 The average length of follow-up in some trials included in this analysis was up to 2 years which may have also contributed to diminution of treatment efficacy.”</p>	

Comments on Topic	
Comment and Source	Response
<p>“Baseline pain values were not taken into account in this study; a difference of 0.9 units for severe pain (8 or greater) is clinically different from the same difference for mild pain (3 or less). Percent change from baseline is an acceptable method for translating magnitude of pain relief, but not mm changes without consideration for baseline. This is another major limitation of the study.”</p>	
<p>“Because pain is a subjective experience, there did not appear to be any consideration for geographical differences in how pain is reported. Trials from some cultures that are known for underreporting pain intensity due to various societal stigmas were also included in this study which might have had an effect on the ES.”</p>	
<p>The commenter describes findings from the 2011 review by Bannuru et al.</p>	
<p>“Prespecified primary safety outcome was a flare-up (defined as hot, painful, swollen knee within 24 to 72 hours after injection) in the injected knee. Six trials with low inter-group heterogeneity (811 patients) contributed to this analysis for flare-ups and the result was not statistically significant.¹ Flare-ups, which are expected and stated in the PIs of all U.S. marketed VS products were not as significant as posited by the authors!⁸⁻¹⁴ SAE was a secondary safety outcome. Only eight trials contributed to the analysis of SAEs reported. Among these eight trials, 27 events occurred in 26 VS patients and 21 events in 14 control patients. A breakdown of the events show GI system disorders 2 in the VS group and 8 among control patients; CV system disorders 5 in VS group and 2 in control group; cancer 6 in VS group; and musculoskeletal system 4 in the VS group and 2 in the control group.¹ It is unknown whether these events were considered related by investigators who assessed them. Although for efficacy outcome the authors attempted to standardize the observation period to 3 months closer to the end of treatment, for safety outcome it appears that the length of observation period was different (0-104 months). Therefore, potentially some SAE could have occurred a</p>	

Comments on Topic	
Comment and Source	Response
<p>year or more after the end of treatment and be unrelated. It is also unclear from the paper what the characteristics of the 14 studies that were used for this analysis. Moreover, they chose to consider eight trials (out of 89 trials that met inclusion criteria) to highlight the SAEs and that might have exaggerated the RR and other statistical parameters. This type of convenience picking of studies within meta-analysis might be a violation of good meta-analytic practice. Of note, the Synvisc-One trial contributed none of the SAEs mentioned in this meta-analysis.⁴ It is also important to note that the article did not discuss SAEs associated with other treatment options for OA knee pain such as NSAIDs, Opioids, and IA steroids.”</p>	
<p>“The authors admitted in their paper that the trial quality was generally low, safety data were not often reported, and they were unclear regarding the probable causes of SAEs and causal mechanisms. . . Adjudication by experts is the industry-wide accepted standard when SAEs become the question of interest. Despite no adjudication was done, the authors prematurely concluded these SAEs attributable to VS treatment and called unfair attention through misinterpreted guidance weighing in on benefit vs. risk.”</p>	
<p>“When stratified by large trials with blinded outcome assessment (18 trials involving 5094 patients), the overall ES was -0.11, (-0.18 to -0.04), and there was low heterogeneity between trials.¹ The Synvisc-One trial data reviewed by the U.S. FDA for marketing registration had an ES of -0.23.”</p>	
<p>“The major limitation of this article is that their analysis and data does not support their strong negative conclusions regarding the VS class.”</p>	
<p>November 30, 2012 Letter from Peter Heeckt, Bioventus</p>	
<p>“As we understand it the proposal is based on the publication of a recent review article, <i>Viscosupplementation for Osteoarthritis of the Knee</i>, authored by Rutjes et. al. in the August 2012 <i>Annals of Internal Medicine</i>. Because there are significant concerns regarding the</p>	<p>Thank you for your comment. No change to topic.</p>

Comments on Topic	
Comment and Source	Response
<p>methodology and conclusions of the authors, we believe this study does not represent credible new evidence regarding the safety and efficacy of Hyaluronic/Viscosupplement products.</p> <p>Our concerns can be broken down into four focus areas: “</p>	<p>Responses to each critique follow.</p>
<p>1. Evaluation of non FDA approved products. “Rutjes et al included 9 additional <u>unapproved</u> products in their analysis. Presumably some of these products are not available in the US market because of their poor safety and efficacy profiles. Please note that HA products differ in formulation, molecular weight, raw material, purity and a host of other factors. We feel evaluation of non FDA approved products severely diminishes the applicability of this research in the US market. A repeat analysis using only FDA approved products would be recommended to draw conclusions for the US market.”</p>	<p>Applicability of the findings in a population with access only to the 6 FDA-approved products will be considered in the report. If the commenter knows of evidence suggesting that the products without FDA approval are less safe than the FDA-approved products, the authors of the report would appreciate receiving citations.</p>
<p>2. Non peer reviewed data included in analysis. “Use of non-peer reviewed data is inadequate and seems counterproductive in the global movement towards evidence based medicine. Credible meta-analyses restrict their inclusion to level 1 evidence, which makes these types of publications compelling in their analysis of large data sets. In this study 33 of 104 reports (32%) were from non-published sources. Unfortunately including data from abstracts, posters, pamphlets, and anonymous sources creates significant questions as to the scientific rigor of this study. Regarding the remaining 72 (68%) reports the authors make no distinction as to whether or not these were peer reviewed publications. This begs the question of exactly how much data was collected from published peer reviewed publications using level 1 evidence as was done in many previously published meta-analyses which the authors roundly criticize.”</p>	<p>The report will consider the influence of unpublished data on the results of this analysis.</p>

Comments on Topic	
Comment and Source	Response
<p>3. Misleading definition of sham vs active controls “The definition of sham intervention and controls is also inadequately addressed. Most orthopedic surgeons acknowledge that injection of saline into the knee is an active treatment which one could argue is an active control. Aspiration of synovial fluid followed by injection of saline is indeed a treatment and can be considered a lavage actively altering the local inflammatory environment and potentially providing temporary pain relief. The use of the word “sham” or placebo implies no active treatment, which in fact is not the case. Use of this word to describe the lavage controls also indicates a fundamental lack of clinical understanding of knee OA and its treatment options.”</p>	<p>The report will consider the influence on the analysis by Rutjes et al. of trials that used saline injection as a control.</p>
<p>4. Comments on adverse events “The implication that hyaluronic acid injections may lead to serious adverse events such as cancer forces the reader to become even more incredulous of the authors’ motivation. The FDA has one of the most robust surveillance systems in the world to monitor for adverse events related to FDA approved products. This surveillance system has not found any significant adverse events related to viscosupplementation products since their first approval more than a decade ago. There has also been no peer reviewed publication on FDA approved products to date which supports or justifies the implications made by the authors. The authors do not distinguish if these adverse events were found in US approved vs non US approved products.”</p>	<p>Guidance from the published literature and from the clinical expert assigned to this topic will be sought for interpretation of reported adverse events.</p>
<p>“Overall this publication serves to confuse and mislead by including data that is not scientifically sound and products that are not FDA approved. There is no new evidence presented on FDA approved products that has not already been reviewed in numerous preceding meta-analyses. As such, the large body of evidence reviewed by the Washington State Health Technology Review Program in 2009-2010 has not substantially changed and we consequently do not see a reason for re-review at this time.”</p>	<p>Thank you for your comment.</p>

Comments on Topic	
Comment and Source	Response
Letter from Louis McIntyre, Advocacy for Improvement in Mobility	
<p>“We would like to comment on the recent Oregon HERC non-coverage decision for viscosupplementation for osteoarthritis of the knee.</p> <p>As noted in your analysis of the evidence concerning Hyaluronic (HA) supplementation, the Washington State Healthcare Authority has issued a limited coverage decision for this modality. We would agree with that decision based upon the Clinical Practice Guideline (CPG) issued by the American Academy of Orthopedic Surgeons (AAOS) on the treatment of osteoarthritis of the knee in 2008. The AAOS CPG recommendation 16 states: “We cannot recommend for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee.” Since the strength of recommendation is inconclusive and the treatment is recognized as safe we concur with Washington State and most private health care insurance carriers that HA treatments should be covered in the limited situations outlined by the HTA. In Oregon, the largest private payer, Regence Blue Cross Blue Shield of Oregon has a published medical coverage policy. National payers with Oregon beneficiaries such as Aetna and United Health Group also provide coverage. “</p> <p>“Medicare and most other private insurers do cover viscosupplementation in osteoarthritic patients with the appropriate symptoms and indications. To deny coverage to Medicaid patients for these procedures creates a potential treatment disparity for the poor and minority patients served by the Medicaid program. Clinical Practice Guidelines are necessary to help improve patient care and make treatment more consistent with the current state of medical knowledge. It is important to have experts examine guidelines to offer necessary insight concerning their relevance and veracity. ”</p>	<p>Thank you for your comments.</p> <p>The cited references will be considered for the report.</p> <p>No change to topic.</p>

Comments on Topic	
Comment and Source	Response
Eric Rugo, Stryker Orthopaedics	
The commenter questions the need for a re-review unless a new trial that fills gaps in the evidence has been published.	Thank you for your comment. Several new RCTs have been published, and the meta-analysis by Rutjes et al. provides new secondary evidence that potentially could change previous conclusions about safety. No change to topic.
Steven St. George, Zimmer, Inc.	
<p>“We do not believe a re-review is warranted at this time, and request that the HTA committee does not re-review this therapy in 2013. The suggested ‘new evidence’ meta analysis by Rutjes et.al. does not , in-fact, add convincing evidence to the comprehensive review done by the HTA committee in May of 2010.”</p> <p>“Zimmer has extensively reviewed the results of the May 2010 review and feels that the HTA committee did a comprehensive job of reviewing the available evidence and arrived at an appropriate decision. Hyaluronic Acid/Viscosupplementation is one of only a handful of non-surgical, low cost treatments that reduce pain and may delay eventual knee arthroplasty. It also represents an important treatment alternative to long term analgesic usage.”</p>	<p>Thank you for your comments.</p> <p>The various critiques of the meta-analysis by Rutjes et al. will be considered in preparation of the update report.</p> <p>No change to topic.</p>
<p>“Rutjes was a comprehensive meta analysis including published, non published and conference proceedings.</p> <ul style="list-style-type: none"> • Very few new studies were included in the article that have become available since the May 2010 WA HTA review. • Inclusion/reliance on non-peer reviewed sources is questionable, especially when used as evidence of publication bias which Rutjes attempts to demonstrate. • Many studies in Rutjes were done outside of the U.S. and concerned products not 	

Comments on Topic	
Comment and Source	Response
<p>approved for use in the U.S.”</p> <p>“Rutjes points out that studies with “sham intervention” typically showed less effect size</p> <ul style="list-style-type: none"> • Sham interventions were typically buffered saline which has demonstrated therapeutic effect • Since the buffered saline arm has therapeutic effect, expected clinical benefit should be smaller than “non-sham” interventions and may explain the lower effect size for larger RCT studies <ul style="list-style-type: none"> ○ It is not surprising to see a small difference between the treatment and control within one well-controlled trial with an active “placebo” control 	

Comments on Draft Key Questions	
Comment and Source	Response
Anke Fierlinger, Ferring	
<p>Key Question #1a The commenter argues that the meta-analysis by Rutjes et al. inappropriately combined data from various HA preparations that differ in source, molecular weight, and structural characteristics and gives the example of cardioselective and noncardioselective Beta blockers to further illustrate the importance of selecting similar studies of similarly acting products for a meta-analysis.</p>	<p>Thank you for your comment. Part of the analysis of the work by Rutjes et al. will include a consideration of whether heterogeneity was detected and appropriate sensitivity analyses were conducted to explore the reasons for heterogeneity. No change to Key Questions.</p>
<p>The commenter suggests a smaller MCID, based on a study of patients treated for knee OA with NSAIDs, than the MCID assumed by Rutjes et al. and shows that patients who received HA injection in the 2009 pivotal EUFLEXXA trial had an average improvement in pain that exceeded the smaller MCID by 30%. The commenter also contrasts this analysis of absolute reduction in pain with the analysis of Rutjes et al. of differences in pain reduction between HA injection and placebo.</p>	<p>Thank you for your comment. The MCID assumed by Rutjes et al. will be discussed in light of other literature on MCID for OA pain relief. Comparing the effect of the treatment of interest with that of placebo is the accepted method of establishing efficacy. No change to Key Questions.</p>
<p>“ . . . intra-articular injection of saline has been repeatedly shown to produce significant reductions in knee pain from baseline.”</p>	<p>This issue will be discussed in the report. Thank you for the cited references.</p>
<p>Key Question #1b “ . . . at least one meta-analysis (Bellamy, 2006) has indicated heterogeneity with respect to the efficacy of these products [different HA preparations] . . . There have been a small number of head-to head- comparisons of different HA preparations (see Colen, 2012, or a review) and results from several studies have indicated that these agents cannot be assumed to have equivalent efficacy . . .” Results from a head-to-comparator trial (Kirchner, 2006) are highlighted.</p>	<p>Thank you for your comment. The authors of the update report will check the review by Bellamy et al. for any evidence of differential effectiveness according to product, and the review by Colen et al. will be added. The Kirchner trial was included in the systematic review by Reichenbach et al.</p>

Comments on Draft Key Questions	
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	(2007), which was covered in the 2010 report. No change to Key Questions.
<p>Key Question #2 The commenter refers to evidence suggesting that “use of cross-linking to achieve higher molecular weight is associated with increased risk for significant adverse events.”</p>	<p>Thank you for your comment. The commenter may be referring to findings by Reichenbach et al., which are covered in the 2010 report. No change to Key Questions.</p>
<p>Key Question #3 “At present, the data from individual clinical studies and pooled analyses are not sufficient to determine whether there are specific patient populations that may derive increased benefit from intra-articular HA injection; additional studies would be needed to determine which patient populations (if any) may have superior responses to this treatment.” “Sensitivity analyses carried out after meta-analyses of clinical trials indicated that the superiority of HA extended across a range of patient subtypes (Bannuru, 2009; Lohmander, 1996). However, other studies have indicated patient characteristics are linked to treatment efficacy. Results from a combined analysis of results from clinical trials suggested that intra-articular HA administration may have its greatest benefit in younger patients with early OA (Wang, 2004).”</p>	<p>Thank you for your assessment of the literature to date. The systematic review by Bannuru et al. will be reviewed again for information on the sensitivity analysis described. The analysis by Wang et al. is included in the 2010 report. No change to Key Questions.</p>
<p>“While no definitive studies linking specific biomarkers to treatment success with intra-articular HA in patients with knee OA have been completed, several references of such potential relationships have been reported.” Several older clinical studies are cited.</p>	<p>Thank you for your comments. The cited studies will be considered for the update report. No change to Key Questions.</p>
<p>Key Question #4 The commenter describes findings from 4 publications.</p>	<p>Thank you for your comments. Three of the cited studies were included in the 2010 report</p>

Comments on Draft Key Questions	
Comment and Source	Response
	<p>or excluded because of poor study design. An in-progress study (Hatoum, 2013) will be included in the update report if it is published during report preparation.</p> <p>No change to Key Questions.</p>
<p>“It is important that one must consider the benefits and risks of alternative therapies for knee OA along with those for intra-articular HA before deciding on an appropriate course of care for a given patient. For example, NSAIDs are among the most commonly used treatments for OA and their efficacy is supported by hundreds of clinical trials. However, the potential for adverse gastrointestinal and cardiovascular events of NSAIDs in a large percentage of patients with OA results in a benefit-risk equation that has prompted clear recommendations against their use in well-defined groups (Lanza, 2009; Antman, 2007).</p> <p>Available evidence strongly supports to obvious conclusion that no single treatment for knee OA will be safe and effective in every patient and that consideration the benefits and risks of all treatments, including differentiation of members within a given ‘class’ of therapies, in conjunction with clinically important individual patient characteristics is the best approach to treatment selection.”</p>	<p>Thank you for your comments.</p> <p>No change to Key Questions.</p>
<p>Peter Heeckt, Bioventus</p>	
<p><i>What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?</i> Hyaluronic Acid/Viscosupplementation is indicated for the treatment of <u>pain</u> in osteoarthritis (OA) of the knee. As such, we propose that the question be modified to read ‘What is the clinical effectiveness of viscosupplementation for treatment of osteoarthritis (OA) knee <u>pain?</u>’”</p>	<p>Thank you for your comment.</p> <p>Improvements in function and quality of life are patient-important outcomes and possible consequences of pain relief that will be covered in addition to pain improvement in</p>

Comments on Draft Key Questions	
Comment and Source	Response
	the report. No change to Key Questions.
<p><i>What are the adverse effects associated with viscosupplementation in patients with OA of the knee?</i></p> <p>“To appropriately assess adverse effects should be categorized and measured by risk level in comparison with alternative common treatments for OA knee pain including NSAIDs, corticosteroids and opioids. This will provide the reviewer with a much fuller picture of the patient risks associated with OA knee pain treatment.”</p>	<p>Thank you for your comment.</p> <p>The report will discuss serious and minor adverse events separately to the extent that the data allow, will provide information on the adverse effects of other treatments in the background section, and will add any new evidence on the comparative rates of serious and minor adverse events.</p> <p>No change to Key Questions.</p>
<p><i>Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?</i></p> <p>“We agree with this question.”</p>	<p>Thank you for your comment.</p> <p>No change to Key Questions.</p>
<p><i>What are the cost implications and cost-effectiveness of this type of product?</i></p> <p>“We interpret the description ‘. . . this type of product’ to include viscosupplements <u>and</u> treatments including NSAIDs, corticosteroids, and opioids. In that context we agree with this question to allow the reviewer to consider the comparative cost implications. We propose the question be reworded to read, ‘<i>What are the cost implications and cost-effectiveness of OA knee pain treatment options?</i>’”</p>	<p>Thank you for your comment.</p> <p>The report is not intended to be a comparative effectiveness review and thus the Key Questions are focused on the intervention of interest. However, studies comparing the cost-effectiveness of viscosupplementation with that of other treatments were included in the 2010 report, and if any such studies have been published since 2010, they will be added in the</p>

Comments on Draft Key Questions	
Comment and Source	Response
	update report. No change to Key Questions.
<p>“In addition to the above questions, we propose an added question, <i>‘What is the risk for an increased rate of total knee arthroplasty procedures if the viscosupplement treatment option is made unavailable?’</i> Please note that the earlier (younger) patients receive a primary TKA, the more likely they will need a revision TKA and a re-revision TKA in their lifetime. This is an important consideration as health care resources become increasingly scarce.”</p>	<p>Thank you for your comment. Topic scoping work conducted for the update report suggested there is little or no evidence regarding the ability of viscosupplementation to delay TKA; thus, this outcome was not added to the PICO. No change to Key Questions.</p>
<p>“Lastly, in the ‘Comparators’ section of the document we request that you change ‘placebo’ to ‘saline injections’. Some studies utilize saline injections but inappropriately refer to it as ‘placebo’.”</p>	<p>Thank you for your comment. In analyzing study results, the update report will consider validity of using saline injection as the placebo. No change to Key Questions.</p>
April 8 Letter from Robert M. Liddell, CDI	
<p>The commenter explains that local radiologists have experience with image guidance of HA injections into very large knees. “For certain patients, we have observed that this procedure works very well for several months, delaying surgical interventions. Indeed, for some patients, this procedure has allowed for total avoidance of surgery.”</p>	<p>Thank you for your comments. No change to Key Questions.</p>
<p>The commenter describes viscosupplementation as a relatively safe procedure when compared with NSAIDs, oral or injectable steroids, and surgery and notes that “Hyaluronic acid is much closer to human chemistry and without the risks of the above, as long as</p>	<p>Evidence regarding the relative safety of viscosupplementation and alternative treatments will be considered in the report.</p>

Comments on Draft Key Questions	
Comment and Source	Response
placement of the agent is precise.”	
“If together we are to conquer the funding challenges we have in health care, we must offer our patients cost-effective options if they are not a surgical candidate, wish to delay surgery, or do not choose to go through the expense and recovery of surgery. Viscosupplementation is one option that has been effective for many of our patients and holds promise to be a low cost, low risk option into the future.”	Evidence regarding cost-effectiveness will be considered in the report.
April 8 Letter from Biji Joseph, Sanofi	
<p>Key Question #1a</p> <p>The commenter proposes changing Key Question #1a to read “What is the clinical effectiveness of viscosupplementation for treatment of OA knee pain?” The rationale for this proposal is that the FDA-approved indication is pain and that improvement in function, stiffness and disease modification are not approved for labeling.</p>	<p>Thank you for your comment.</p> <p>Lack of FDA approval of outcomes other than pain for purposes of labeling does not suggest that other patient-important outcomes such as improved function would be irrelevant. Any new evidence concerning the outcomes specified in the PICO statement (pain, function, quality of life, adverse events) will be considered in the update; disease modification is not an outcome of interest.</p> <p>No change to Key Questions.</p>
<p>Key Question #1b</p> <p>“There have been numerous citations citing statistically and possibly clinically important differences in favor of high molecular weight, cross-linked product hylan G-F 20.”</p>	<p>Thank you for your comment.</p> <p>New evidence on the comparative effectiveness of different viscosupplementation products will be considered.</p> <p>No change to Key Questions.</p>

Comments on Draft Key Questions	
Comment and Source	Response
<p>Key Question #2 “Considering that OA is a disease of pain and disability, and not life-threatening, extreme risks in exchange for clinical improvements are not well accepted by the medical and patient community. There has been ongoing and recent controversy and acute interest surrounding systemic AEs for the widely used systemic medications to treat OA – acetaminophen, NSAIDs/COS-2 inhibitors, and opioids. Adverse effects have been documented as minimal for the VS class and the risk/benefit ratio makes the class an acceptable option for the treatment of OA knee pain.”</p>	<p>Thank you for your comment. The PICO statement lists NSAIDs, corticosteroid injection, and oral pain medications as comparators of interest and thus new evidence of the comparative safety of viscosupplementation and these other treatments will be considered. No change to Key Questions.</p>
<p>Key Question #3 “To our knowledge, no group has published a class-level analysis of potential heterogeneity in response to VS by special population. Per approved labeling, pivotal clinical trials for approved VS included patient age ranges of 41-90. For those products not including age ranges in their labels, the mean ages of trial participants were between 60 and 65. To our knowledge, there are not publications that have definitively proven that older patients or patients with advanced radiographic have a reduced VS analgesic effect. In addition, we are unaware of any published study in which the authors have been able to predict, via demographic factors alone, which patients will respond to VS. No diminution in effect or safety issues was found to be associated with any specific population.”</p>	<p>Thank you for your comment. No change to Key Questions.</p>
<p>Key Question #4 “The management of knee OA is not optimal and usually results in total knee replacement (TKR). The cost of TKR is expensive and it is a morbid procedure for many patients. There have been reports in the literature of delaying of TKR in some patients after being on VS treatment. A comprehensive cost effectiveness analysis inclusive of all modalities in the treatment of OA knee pain has not been done.”</p>	<p>Thank you for your comment. No change to Key Questions.</p>

Comments on Draft Key Questions	
Comment and Source	Response
April 8 Letter from Samir Bhattacharyya, Suresh Aravind, Brad Bisson, and Brooks Story; DePuy Mitek, Inc.	
<p>Key Question #1a “Since FDA approved viscosupplementation treatments are indicated for the treatment of pain in osteoarthritis (OA) of the knee, we propose that the question be modified as follows: <i>What is the clinical effectiveness of viscosupplementation for treatment of pain associated with OA of the knee?</i>”</p>	<p>Thank you for your comment. Lack of FDA approval of outcomes other than pain for purposes of labeling does not suggest that these other outcomes are not relevant. Any new evidence concerning the outcomes specified in the PICO statement (pain, function, quality of life, adverse events) will be considered in the update. No change to Key Questions.</p>
<p>Key Question #2 The commenters recommend changing Key Question #2 to a part a: “<i>What are the adverse effects associated with viscosupplementation in patients treated for pain due to OA of the knee?</i>”</p>	<p>Thank you for your comment. The question as worded (<i>What are the adverse effects associated with viscosupplementation in patients with OA of the knee?</i>) simply defines the population of interest without regard to therapeutic intent. No change to Key Questions.</p>
<p>“Some treatment alternatives for OA knee pain are NSAIDs, intra-articular steroids and opioids. A comparative analysis of adverse events between viscosupplementation and these treatment alternatives will provide a comprehensive risk-benefit assessment in this regard. We propose adding a question in this section as follows: <i>What is the adverse effect profile of viscosupplementation compared to other treatments, including but not limited to NSAIDs, intra-articular steroids, and opioids, available for patients with OA knee pain?</i>”</p>	<p>Thank you for your comment. Since these other treatments are named as comparators in the PICO statement, it is not necessary to change the Key Question to assure they are considered. No change to Key Questions.</p>

Comments on Draft Key Questions	
Comment and Source	Response
<p>Key Questions #3 and #4 The commenters agree with Key Questions #3 and #4.</p>	<p>Thank you for your comment. No change to Key Questions.</p>
<p>Additional Key Question The commenters recommend adding the following question: <i>“What are other safe, effective, and cost-effective treatment options available if patients do not have access to viscosupplementation products?”</i></p>	<p>Thank you for your comment. Any comparative data regarding viscosupplementation and other nonsurgical options will be included when answering Key Questions 1-4, in accordance with the PICO. No change to Key Questions.</p>
<p>April 8, 2013 Letter from Steven St. George, Zimmer</p>	
<p>Key Question #1a “We agree that this is an appropriate question however we feel it is important to clarify that HA/Viscosupplementation is a treatment of pain associated with OA of the knee, not a treatment for OA.”</p>	<p>Thank you for your comment. The outcomes of interest that are specified for this topic reflect the fact that HA injections are intended to reduce pain, which may have an effect on function and QOL. No change to Key Questions.</p>
<p>Key Question #1b “We agree with this question.”</p>	<p>Thank you for your comment. No change to Key Questions.</p>
<p>Key Question #2 “We agree with this question, however, comparisons with other knee osteoarthritis treatments should be highlighted. These should be categorized based on risk levels and should include mortality and morbidity rates. For example there are well documented NSAID safety issues.” The commenter suggests adding “compared with alternative treatments” to the question.</p>	<p>Thank you for your comment. Since the PICO statement specifies other treatments as comparators of interest, the safety of viscosupplementation compared with the safety of other treatments will be addressed.</p>

Comments on Draft Key Questions	
Comment and Source	Response
	No change to Key Questions.
<p>Key Question #3 “We agree with this question.”</p>	<p>Thank you for your comment. No change to Key Questions.</p>
<p>Key Question #4 “We agree with this question, however, cost-effectiveness should appropriately be looked at through the same lens as other pain medications. That is, HA/Viscosupplements are indicated specifically for reducing pain and therefore should be measured vs. NSAIDs, opioids, etc.” The commenter suggests modifying the question to read “cost-effectiveness of treatment options for pain associated with OA?”</p>	<p>Thank you for your comment. The commenter seems to be suggesting that cost-effectiveness should be considered in terms of cost per unit of pain improvement rather than the typical cost per QALY. Any and all cost-effectiveness data will be considered. No change to Key Questions.</p>
<p>Proposed new question: “5. In the hypothetical absence of Hyaluronic Acid/Viscosupplement therapy, what safe and effective evidence-based alternative therapies are available?”</p>	<p>Thank you for your comment. The existing Key Questions and PICO for the evidence report have been designed to determine whether viscosupplementation has been shown to be safe and effective and how it compares with alternative treatments in terms of safety and effectiveness. The proposed question might be relevant to policymaking, but does suggest potential evidence that would otherwise be missed. No change to Key Questions.</p>

Date: April 8, 2013

To: Washington State Health Technology Assessment (WSHTA)

Re: Public comments on the Draft Key Questions: Hyaluronic Acid/Viscosupplementation

We appreciate the opportunity to comment on the draft key questions for the review of Hyaluronic Acid / Viscosupplementation for treatment of pain in osteoarthritis (OA) of knee. Please see below our comments:

1a. What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

Since FDA approved viscosupplementation treatments are indicated for the treatment of pain in osteoarthritis (OA) of the knee, we propose that the question be modified as follows:

What is the clinical effectiveness of viscosupplementation for treatment of pain associated with OA of the knee?

1b. Do different viscosupplementation products vary in effectiveness?

We agree with this question.

2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

The above question needs to be modified as follows:

2a. What are the adverse effects associated with viscosupplementation in patients treated for pain due to OA of the knee?

Some treatment alternatives for OA knee pain are NSAIDs, intra-articular steroids and opioids. A comparative analysis of adverse events between viscosupplementation and these treatment alternatives will provide a comprehensive risk-benefit assessment in this regard. We propose adding a question in this section as follows:

2b. What is the adverse effect profile of viscosupplementation compared to other treatments, including but not limited to NSAIDs, intra-articular steroids, and opioids, available for patients with OA knee pain?

3. Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

We agree with this question.

4. What are the cost implications and cost-effectiveness of this type of product?

We agree with this question.

In addition to the suggestions above, if allowable, we propose to add another question for WSHTA to consider:

5. What are other safe, effective, and cost-effective treatment options available if patients do not have access to viscosupplementation products?

We hope that our suggestions add value to your program. If you have any questions, please do not hesitate to contact us anytime.

Sincerely,

Samir Bhattacharyya, PhD
World Wide Director, Market Access

Suresh Aravind, MD, MBA
Vice President, Strategic Medical Affairs

Brad Bisson, MPH
Manager, Medical and Scientific Affairs

Brooks Story, PhD
Research Fellow, Research & Development

KEY QUESTIONS AND RESPONSES RELATIVE TO THE WASHINGTON STATE HEALTH CARE AUTHORITY

Ferring Pharmaceuticals Inc. is a research-driven biopharmaceutical company devoted to developing and marketing innovative products for a wide range of conditions including the treatment of osteoarthritis (OA). Euflexxa, a bioengineered, non-avian, straight chain hyaluronic acid is available in the US for the treatment of OA pain in patients who do not adequately respond to conservative therapy and simple analgesics.

We appreciate the opportunity to respond to the Washington State Health Care Authority "key questions" regarding viscosupplementation for knee OA.

We maintain that viscosupplementation with hyaluronan (HA) is an effective and safe option for patients not achieving adequate pain relief with other interventions or who cannot tolerate adverse events associated with acetaminophen, nonsteroidal anti-inflammatory drugs, or intra-articular corticosteroid injections, or are unwilling to accept the well-known risks associated with these drugs (AASLD, 2012; Dubois, 2004; Garcia Rodriguez, 2001; Hennekens, 2008; Lanus, 2006; Larson, 2005; McGarry, 2011). Our responses to the questions put forward are as follows.

1a. What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

The questions being raised regarding the clinical effectiveness of viscosupplementation for treatment of OA of the knee can be traced to the conclusions reported from the meta-analysis carried out by Rutjes et al which stated in part that, "In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events" (Rutjes, 2012). Reliance on this analysis relative to formulating an authoritative opinion as to efficacy is misplaced. Quantitative synthesis and meta-analyses can be valuable tools used to help identify trends in drug and device efficacy and safety. However, when there is substantial heterogeneity among studies, interpretation of results from meta-analyses is difficult and are questionable in providing better evidence regarding efficacy than review of well-designed randomized controlled trials which are deemed the "gold standard" in clinical science to establish safety and efficacy.

One critical point in meta-analysis is selection of studies and those included should be as similar as possible with respect to a variety of parameters, including treatment type (Walker, 2008). For example, it makes little sense to carry out a meta-analysis that combines results from cardioselective and noncardioselective β -blockers if the question being addressed is safety of β -receptor blockade in patients with heart failure and respiratory disease (Salpeter, 2005; Hawkins, 2011; Self, 2012). While the two groups of drugs are superficially similar, they have different effects on pulmonary function (Hawkins, 2011). We suggest that the same is true of HA preparations. While these agents are often considered as a homogeneous class, they actually differ substantially in their source, molecular weight, and structural characteristics (Migliore, 2008) all of which impact an analysis of their respective clinical benefits and risks. These differences have been acknowledged in a prior meta-analysis, which concluded that, "It is of note that the magnitude of the clinical effect, as expressed by the WMD [weighted mean difference] and standardised mean difference (SMD) from the RevMan 4.2 output, is different for different products..." (Bellamy, 2006).

While it is clear from the literature that not all hyaluronan (HA) preparations have demonstrated significant efficacy versus placebo in every clinical trial (eg, Kul-Panza, 2010; Jorgensen, 2010; Lundsgaard), it is equally clear that others have demonstrated consistent efficacy versus placebo and have also provided clinically significant benefit in decreasing pain in patients with knee OA.

EUFLEXXA® (1% sodium hyaluronate) is a highly purified, non-avian derived, high molecular weight HA, indicated for treatment of OA knee pain in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (eg, acetaminophen) (EUFLEXXA PI, 2011). Clinical trial results with EUFLEXXA have shown that, when used as indicated, EUFLEXXA is significantly superior to placebo and provides clinically meaningful pain relief in patients with knee OA.

One of the pivotal clinical trials supporting EUFLEXXA for treatment of OA knee pain was a randomized, double-blind, multicenter, saline-controlled study that included 588 patients who received 3 weekly intra-articular injections of EUFLEXXA or saline and were followed for 26 weeks. The primary efficacy outcome was change in pain from baseline to week 26 following a 50-foot walk test, measured via a 100-mm visual analog scale (VAS) (Altman, 2009). In the EUFLEXXA group, the mean VAS scores decreased by 25.7 mm, compared with 18.5 mm in the saline control group ($P=0.002$). Thus, EUFLEXXA is significantly superior to placebo in decreasing OA knee pain and these results supported its approval by the US Food and Drug Administration for this indication.

The reduction in pain from baseline with EUFLEXXA was clinically meaningful. A large-scale evaluation that included 603 patients with knee OA specifically addressed the question of what constitutes a minimal clinically important improvement (MCII) in knee OA pain by combining results obtained with a 100-mm VAS scale and responses to direct questions about improvement in pain with nonsteroidal anti-inflammatory drug treatment (Tubach, 2005). Results from this careful analysis indicated that the MCII for pain measured in the same way as in the study of EUFLEXXA was 19.9 mm. Thus, the results from the pivotal trial of EUFLEXXA showed that treatment with this HA preparation produced a decrease in pain that exceeded the MCII by about 30%. The reduction in pain with the saline control did not achieve the MCII established by the benchmarking study. Results from this study also indicated that improvements observed with EUFLEXXA exceeded the established MCIs for both WOMAC function and Patient Global Assessment (Altman, 2009; Tubach, 2005).

We believe that the outcome reported above differs from and highlights the shortcomings of the meta-analysis carried out by Rutjes et al (2012) for two (2) reasons. First, the clinical trial used a high molecular weight non-cross-linked HA preparation. The results reported by Rutjes et al (2012) show that the point estimates for effect sizes for high and low molecular weight HA preparations were different, but that this heterogeneity was not significant ($P=0.110$ for the interaction). Nevertheless, the point estimates for the high and very high molecular weight HAs exceeded the minimal clinically important difference of -0.37 employed in the analysis, while the point estimates for low molecular weight preparations did not. Second, the evaluation summarized here considers the absolute reduction in pain from baseline with EUFLEXXA for definition of MCII (as specified by Tubach, 2005) rather than effect size versus placebo (as was used by Rutjes, 2012).

We believe that these two (2) differentiating aspects of our analysis of the clinical trial are reasonable because of the heterogeneity of HA preparations (Migliore, 2008; and see below) and that intra-articular injection of saline has been repeatedly shown to produce significant reductions in knee

pain from baseline (eg. Loughnan, 2009; Frias, 2004; Ravaud, 1999; Dawes, 1987; Wright, 1960; Miller, 1958; Rosseland, 2003), and thus should be considered as an active control rather than a true placebo. In their analysis of studies of HA for knee OA, Colen et al. (2012) noted that, "However, if saline may have an effect on the symptoms we might be making the wrong comparison, causing the difference [between HA and placebo] to seem smaller than it in fact is."

In summary, results for EUFLEXXA show that it is significantly superior to an active control that has been shown to provide significant relief from knee pain in multiple studies and that the pain relief with EUFLEXXA is clinically significant.

1b. Do different viscosupplementation products vary in effectiveness?

As noted above, there are differences in the characteristics of HA preparations with respect to origin, molecular weight, and chemical cross-linking (Migliore, 2008); and at least one meta-analysis (Bellamy, 2006) has indicated heterogeneity with respect to the efficacy of these products. This heterogeneity is further reflected by the fact that some preparations have failed to demonstrate significant efficacy versus intra-articular saline (Kul-Panza, 2010; Jorgensen, 2010; Lundsgaard, 2008) while others have demonstrated consistent efficacy versus this active control (e.g., Kirchner, 2006; Altman, 2009; Navarro-Sarabia, 2011). There have been a small number of head-to-head comparisons of different HA preparations (see Colen, 2012 for a review) and results from several studies have indicated that these agents cannot be assumed to have equivalent efficacy (eg. Wobig, 1999; Kirchner, 2006; Raman, 2008; Chou, 2009; Berenbaum, 2012).

Perhaps the best support for this point comes from a 12-week, prospective, multicenter, randomized double-blind trial that compared the efficacy and safety of EUFLEXXA and Synvisc® (an avian-derived product in which high molecular weight is achieved by chemical cross-linking) in 321 patients with confirmed knee OA. In this trial, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (VAS) was the primary effectiveness measure. Both products were administered via 3 weekly injections, with follow-up evaluations at weeks 3, 6, and 12. Acetaminophen was permitted as rescue medication and quantitated by pill counts. At the study endpoint, 63% of patients in the EUFLEXXA group were symptom free compared to 52% in the Synvisc group ($P=0.038$). This difference between groups with respect to symptom-free patients for the WOMAC pain subscale was confirmed by evaluating the percentage of patients with an average WOMAC function subscale score <20 mm at week 12: 64.3% for the EUFLEXXA group versus 47.5% for the Synvisc group ($P=0.003$). In addition, significant differences favored EUFLEXXA for the number of patients requiring acetaminophen ($P=0.013$) and patient global satisfaction evaluations ($P=0.03$) (Kirchner, 2006).

2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

Hyaluronans have a generally acceptable safety profile and the most common adverse events reported have been injection site reactions (Reichenbach, 2007; Huskisson, 1999). It has been estimated that adverse reactions occur in $<3\%$ of injections and that they are almost always local and generally resolve over 1–2 days (Watterson, 2000). However, all HA preparations cannot be considered together with respect to safety. This point is strongly supported by results from the meta-analysis (Rutjes, 2012) that prompted this review. This analysis included 89 trials, but only 6 indicated that HA increased the risk

for flare-ups (hot, painful, swollen knee within 24–72 hours after injection) and 14 trials showed that viscosupplementation increased the risk for serious adverse events (events resulting in inpatient hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality of offspring, life-threatening events, or death) (Rutjes, 2012). Even though the listed results do not distinguish between treatment-related and unrelated adverse events previous studies have suggested that use of cross-linking to achieve higher molecular weight is associated with increased risk for significant adverse events.

Results from the above-described comparison of Synvisc and EUFLEXXA indicated a significant difference in the risk for local reactions between the products in that 15 effusions were reported after injection in 8.1% of patients who received the avian preparation versus 0.6% of those treated with the bioengineered HA (P=0.0015). The safety profile of EUFLEXXA is further demonstrated by results from the FLEXX extension study in which patients from the 26-week FLEXX trial (Altman, 2009) received a second series of three EUFLEXXA injections and followed for an additional 26 weeks. No joint effusions were observed of a total of 52 weeks of follow-up (Altman, 2011). The most common adverse events related to EUFLEXXA injections reported in 12- and 26-week clinical studies were arthralgia, back pain, pain in extremity, musculoskeletal pain, and joint swelling. In an open-label extension of the 26-week clinical study with repeat series of injections, the most common adverse events related to EUFLEXXA at Week 52 were arthralgia and joint swelling.

See below Euflexxa Indication and Important safety information (Package insert is attached to with the submitted document).

Indication

EUFLEXXA[®] (1% sodium hyaluronate) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen).

EUFLEXXA is contraindicated in patients who have a known hypersensitivity to hyaluronate preparations or who have knee joint infections, infections, or skin disease in the area of the injection site.

Important Safety Information

EUFLEXXA should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use skin disinfectants for skin preparation that contain quaternary ammonium salts.

Do not inject intravascularly due to potential for systemic adverse events. The safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee have not been studied. Remove any joint effusion prior to injecting. Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA.

Results from other studies have also indicated a relationship between cross-linking to achieve high molecular weight with avian-derived HA preparations and increased risk for local adverse reactions. Results from a study of patients with knee OA treated with this type of preparation indicated that 1 patient experienced a severe pseudoseptic reaction (Juni, 2007). Other studies have also raised concerns regarding localized inflammatory reactions with cross-linked hyaluronan or hylan products (Rees, 2001; Martens, 2001; Leopold, 2002; Morton, 2003; Goldberg, 2004). In particular, results from animal experiments that evaluated 3 avian-derived HA preparations indicated that injection of each of them into

mice resulted in a significant inflammatory response characterized by increased cellularity. One injection resulted in an immune response (Ottaviani, 2007).

3. Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

At present, the data from individual clinical studies and pooled analyses are not sufficient to determine whether there are specific patient populations that may derive increased benefit from intra-articular HA injection; additional studies would be needed to determine which patient populations (if any) may have superior responses to this treatment.

Sensitivity analyses carried out after meta-analyses of clinical trials indicated that the superiority of HA extended across a range of patient subtypes (Bannuru, 2009; Lohmander, 1996). However, other studies have indicated patient characteristics are linked to treatment efficacy. Results from a combined analysis of results from clinical trials suggested that intra-articular HA administration may have its greatest benefit in younger patients with early OA (Wang, 2004). Results from this meta-analysis indicated that patients >65 years of age and those with the most advanced stages of arthritic change (ie, complete loss of joint space) were less likely to demonstrate improvement with HA therapy than younger patients with less advanced disease (Wang, 2004). In a large, randomized study that assessed the disease-modifying effects of HA in knee OA, it was shown that viscosupplementation, compared with placebo, significantly reduced the radiographic progression of joint space loss in the subset of patients with a higher joint space area at study entry (Jubb, 2003).

There has been great interest, across virtually all therapeutic areas, in biomarkers, which can be defined as predictive markers which are associated with likelihood of a particular clinical outcome in response to a specific therapy or class of treatments (Galanis, 2001). While no definitive studies linking specific biomarkers to treatment success with intra-articular HA in patients with knee OA have been completed, several references of such potential relationships have been reported. Results from a small study of 36 patients with knee OA indicated that higher baseline levels of aggrecans, chondroitin 6-sulfate and chondroitin 4-sulfate were associated with greater improvements in Japanese Orthopaedic Association score after treatment with an HA preparation (Sugimoto, 2006). Similar results for chondroitin 6-sulfate and chondroitin 4-sulfate were reported for 16 patients with knee OA who received intra-articular HA (Kobayashi, 2004). A third study also showed that elevated baseline levels of synovial chondroitin 4-sulfate and tenascin-C were associated with greater reductions in pain measured by VAS in patients who received intra-articular HA injections (Hasegawa, 2008). Results from a study of 32 patients with mild to moderate knee OA indicated that higher baseline levels of HA in the synovial fluid were associated with increased probability of achieving $\geq 50\%$ improvement in pain or function or a ≥ 20 unit improvement on the WOMAC questionnaire (Anandacoomarasamy, 2008). Results from another study of 41 patients with knee OA who were treated with HA indicated that reductions in synovial fluid concentrations of interleukin-6 were significantly associated with clinical improvement (Sezgin, 2005).

4. What are the cost implications and cost-effectiveness of this type of product?

Intra-articular injection of HA has been shown to have significant pharmacoeconomic benefit that is primarily related to the ability of this treatment to delay total knee arthroplasty (TKA). Results of a

pharmacoeconomic analysis of intra-articular HA for knee OA indicated that 3-year savings associated with adding one (1) or more courses of intra-articular HA to the standard treatment pathway for OA of the knee was \$8,810,771. This economic benefit resulted from the effect of intra-articular HA in decreasing progression of patients to TKA; 808 surgeries were avoided in this analysis (Waddell, 2001). Results from another more recent analysis indicated that intra-articular HA delayed TKA by an average of 772 days and that the average cost for achieving this delay was \$1420 (Waddell, 2007). At the time when this study was performed, the cost of knee replacement surgery was reported to be \$24,045 (Waddell, 2007). A third economic analysis conducted in Thailand also indicated that intra-articular HA was cost effective as a result of its ability to delay the requirement for TKA (Turajane, 2007). Results from another study that did not consider cost associated with knee replacement indicated that intra-articular injection of HA was clinically more effective than conventional treatment and that it was no more expensive when both medication and sick leave costs were considered (Kahan, 2003). Results from other less formal economic analyses have also supported the economic utility of intra-articular HA for treatment of patients with knee OA (Mazieres, 2007; Dagenais, 2006).

A recent study determined the cost-effectiveness of intra-articular injections of EUFLEXXA for treatment of patients with OA of the knee from a healthcare payer's perspective. A decision analytic model was used to compare EUFLEXXA-treated patients using the patient's own baseline as the historical control. This choice was based on the assumption that, in the absence of treatment with EUFLEXXA, patients would have continued treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics and would not have experienced a change in their utility scores over the 1-year study period. The model used clinical trial data from patients who received two courses of EUFLEXXA treatment (Altman, 2009; Altman, 2011). Health Utilities Index Mark 3 (HUI-3) utility scores were derived at several time points from WOMAC scores. HUI-3 scores were then used to derive quality-adjusted life years (QALYs) gained from EUFLEXXA. Published total costs for 12 months of conventional treatment with NSAIDs and analgesics (\$3693) were assigned to the historical control cohort. Costs for the EUFLEXXA group included EUFLEXXA treatment costs and administration fees, plus one half of conventional treatment costs. Cost-effectiveness ratios were expressed as average and incremental costs per QALY. One-way sensitivity analyses were performed using the 95% confidence interval of QALYs gained in EUFLEXXA, and $\pm 20\%$ of EUFLEXXA treatment and conventional treatment costs. Of 214 patients who completed the 2 courses of EUFLEXXA treatment, the average utility gain was 0.163 QALY (95% CI, -0.162~0.488) over the 52-week study period. The total treatment costs were \$3,043 for the EUFLEXXA group and \$3,693 for the historical cohort group. Because the EUFLEXXA was both less costly and more effective than conventional treatment, EUFLEXXA was the dominant treatment strategy. Sensitivity analyses showed EUFLEXXA to be the dominant treatment strategy except when BioHA was at the lower end of the 95% CI value (Hatoum, 2013).

Conclusion

We understand that the aim of the questions raised by the Washington State Health Care Authority was to gain greater understanding of the efficacy, safety, and cost effectiveness of intra-articular HA in patients with knee OA and we have focused our answers on these issues. However, we suggest that a too narrow review of the benefit-risk equation for HA undertaken in isolation may not provide all of the information needed to support fully informed treatment decisions and establish an accurate assessment of the benefits, risks and cost effectiveness of this therapy. It is important that one must consider the benefits and risks of alternative therapies for knee OA along with those for intra-articular HA before deciding on an appropriate course of care for a given patient. For example, NSAIDs

are among the most commonly used treatments for OA and their efficacy is supported by hundreds of clinical trials. However, the potential for adverse gastrointestinal and cardiovascular events of NSAIDs in a large percentage of patients with OA results in a benefit-risk equation that has prompted clear recommendations against their use in well-defined groups (Lanza, 2009; Antman, 2007).

Available evidence strongly supports to obvious conclusion that no single treatment for knee OA will be safe and effective in every patient and that consideration the benefits and risks of all treatments, including differentiation of members within a given "class" of therapies, in conjunction with clinically important individual patient characteristics is the best approach to treatment selection

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April 8, 2013

Health Care Authority
626 8th Ave SE
P.O. Box 42712
Olympia, WA 98504-2712

Dear Ms. Masters,

Thank you for the opportunity to comment on the Draft Key Questions for the re-review of Hyaluronic Acid / Viscosupplementation. Our comments on the questions are below:

What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

Hyaluronic Acid / Viscosupplementation is indicated for the treatment of pain in osteoarthritis (OA) of the knee. As such, we propose that the question be modified to read "What is the clinical effectiveness of viscosupplementation for treatment of osteoarthritis (OA) knee pain?"

What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

To appropriately assess adverse effects should be categorized and measured by risk level in comparison with alternative common treatments for OA knee pain including NSAIDs, corticosteroids and opioids. This will provide the reviewer with a much fuller picture of the patient risks associated with OA knee pain treatment.

Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

We agree with this question.

What are the cost implications and cost-effectiveness of this type of product?

We interpret the description "...this type of product" to include viscosupplements and and treatments including NSAIDs, corticosteroids, and opioids. In that context we agree with this question to allow the reviewer to consider the comparative cost implications. We propose that the question be reworded to read, "What are the cost implications and cost effectiveness of OA knee pain treatment options?"

In addition to the above questions, we propose an added question, "***What is the risk for an increased rate of total knee arthroplasty procedures if the Viscosupplement treatment option is made unavailable?***"

Please note that the earlier (younger) patients receive a primary TKA, the more likely they will need a revision TKA and a re-revision TKA in their lifetime. This is an important consideration as health care resources become increasingly scarce.

Lastly, in the "Comparators" section of the document we request that you change "placebo" to "saline injections". Some studies utilize saline injections but inappropriately refer to it as "placebo".

Again, thank you for the opportunity to comment on the Draft Key Questions

Sincerely,



Peter Heeckt, MD, PhD
Chief Medical Officer

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April 8, 2013

Josh Morse, MPH
Program Director
Washington Health Technology Assessment Program
676 Woodland Square Loop SE
Olympia, WA 98504-2712

Dear Mr. Morse:

Sanofi Medical Affairs recently became aware of Washington State HTA's request for public comment regarding the draft key questions for the re-review of hyaluronic acid/viscosupplement class. Sanofi is the manufacturer and marketer of a viscosupplement (VS) product with the generic name hylan G-F 20. It is sold in two forms: SYNVISIC® (3 injections per course) and Synvisc-One® (1 injection per course). Our comments on the questions are below:

1a: What is the clinical effectiveness of viscosupplementation for treatment of OA of the knee?

The indication currently approved by the US FDA for all VS products can be summarized as follows: the treatment of pain due to OA of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen). Improvement in function, stiffness, and disease modification are not approved labeling for any VS in the US. We propose that the question be modified to read "What is the clinical effectiveness of viscosupplementation for treatment of OA knee pain?"

1b: Do different viscosupplementation products vary in effectiveness?

There have been numerous citations citing statistically and possibly clinically important differences in favor of high molecular weight, cross-linked product hylan G-F 20.

2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee?

Considering that OA is a disease of pain and disability, and not life-threatening, extreme risks in exchange for clinical improvements are not well accepted by the medical and patient community. There has been ongoing and recent controversy and acute interest surrounding systemic AEs for the widely used systemic medications to treat OA- acetaminophen, NSAIDs/COX-2 inhibitors, and opioids. Adverse effects have been documented as minimal for the VS class and the risk/benefit ratio makes the class an acceptable option for the treatment of OA knee pain.



3. Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments?

To our knowledge, no group has published a class-level analysis of potential heterogeneity in response to VS by special population. Per approved labeling, pivotal clinical trials for approved VS included patient age ranges of 41-90. For those products not including age ranges in their labels, the mean ages of trial participants were between 60 and 65. To our knowledge, there are no publications that have definitively proven that older patients or patients with advanced radiographic have a reduced VS analgesic effect. In addition, we are unaware of any published study in which the authors have been able to predict, via demographic factors alone, which patients will respond to VS. No diminution in effect or safety issues was found to be associated with any specific population.

4. What are the cost implications and cost-effectiveness of this type of product?

The management of knee OA is not optimal and usually results in total knee replacement (TKR). The cost of TKR is expensive and it is a morbid procedure for many patients. There have been reports in the literature of delaying of TKR in some patients after being on VS treatment. A comprehensive cost effectiveness analysis inclusive of all modalities in the treatment of OA knee pain has not been done.

If you have further questions after reviewing this information, please feel free to contact me at 617-761-8206. Thank you for the opportunity to comment on the Draft Key Questions.

Sincerely,

A handwritten signature in black ink that reads "Biji Joseph". The signature is written in a cursive style and is positioned above a horizontal line.

Biji Joseph, PharmD, MBA
Director, Medical Affairs

CENTER FOR
DIAGNOSTIC IMAGING

April 8, 2013

Health Technology Assessment Program
c/o Program Director Josh Morse, MPH
via email to shtap@hcawa.gov
RE: Viscosupplementation

Dear HTA Advisers:

On behalf of Center for Diagnostic Imaging – Puget Sound and the 15 sub-specialized, interventional radiologists who partner with CDI at our eight offices in the Puget Sound region, thank you for the opportunity to provide clinical practice input into the discussion regarding viscosupplementation.

Our local radiology practices have experience with this interventional procedure for certain, complex patients with osteoarthritis of the knee. This is usually because of the need for image guidance for patients with very large knees. Employing fluoroscopy allows assurance of, and documents that, the pharmaceutical agent is injected into the joint. Without appropriate image guidance to assure placement of the viscosupplement into the joint of these complex patients, there is a higher risk for an inflammatory reaction and basic failure of the intended relief.

For certain patients, we have observed that this procedure works very well for several months, delaying surgical interventions. Indeed, for some patients, this procedure has allowed for total avoidance of surgery.

We expect that as the pharmaceutical products evolve and decrease in price, this procedure will be beneficial for specific patients with osteoarthritis of other joints. Because of anatomical considerations, image guidance should be used for patients who choose this procedure for hip or shoulder osteoarthritis relief.

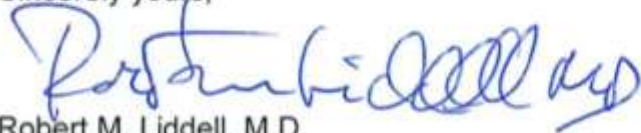
As you deliberate, we encourage you to consider two very practical issues, as we do, with the patients referred to us for this procedure:

1. This is a relatively safe procedure, compared to other tools musculoskeletal specialists currently have in their tool box. Nonsteroidal anti-inflammatory drugs have many serious adverse effects; oral and injectable steroids, used repeatedly, can permanently damage joint cartilage, or have other serious health consequences. Surgery brings risks and costs that are fully explored in peer-reviewed literature, along with extensive recovery time and productivity loss for the patient. Hyaluronic acid is much closer to human chemistry and without the risks of the above, as long as placement of the agent is precise.

2. If together we are to conquer the funding challenges we have in health care, we must offer our patients cost-effective options if they are not a surgical candidate, wish to delay surgery, or do not choose to go through the expense and recovery of surgery. Viscosupplementation is one option that has been effective for many of our patients and holds promise to be a low cost, low risk option into the future.

Thank you for considering our comments, which are based on our commitment to best clinical practice and our practical clinical experience. Please do not hesitate to contact me if I can be further helpful.

Sincerely yours,



Robert M. Liddell, M.D.
CDI National Section Leader – MSK subspecialty

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Advocacy for Improvement in Mobility

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RE: Coverage Guidance: Viscosupplementation for Osteoarthritis of the Knee

Dear WSHCA HTA,

Advocacy for the Improvement in Mobility (AIM) is a non-profit corporation dedicated to ensuring patient access to appropriate, high quality musculoskeletal health care. We would like to comment on the recent Oregon HERC non-coverage decision for viscosupplementation for osteoarthritis of the knee.

As noted in your analysis of the evidence concerning Hyaluronic (HA) supplementation, the Washington State Healthcare Authority has issued a limited coverage decision for this modality. We would agree with that decision based upon the Clinical Practice Guideline (CPG) issued by the American Academy of Orthopedic Surgeons (AAOS) on the treatment of osteoarthritis of the knee in 2008. The AAOS CPG recommendation 16 states: "We cannot recommend for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee." Since the strength of recommendation is inconclusive and the treatment is recognized as safe we concur with Washington State and most private health care insurance carriers that HA treatments should be covered in the limited situations outlined by the HTA. In Oregon, the largest private payer, Regence Blue Cross Blue Shield of Oregon has a published medical coverage policy. National payers with Oregon beneficiaries such as Aetna and United Health Group also provide coverage. Attached are the Regence and Aetna coverage policies for viscosupplementation.

Medicare and most other private insurers do cover viscosupplementation in osteoarthritic patients with the appropriate symptoms and indications. To deny coverage to Medicaid patients for these procedures creates a potential treatment disparity for the poor and minority patients served by the Medicaid program. Clinical Practice Guidelines are necessary to help improve patient care and make treatment more consistent with the current state of medical knowledge. It is important to have experts examine guidelines to offer necessary insight concerning their relevance and veracity. Attached, please find three additional reference articles HERC might consider in finalizing coverage guidance. We would be happy to advise the HERC on further guidelines concerning musculoskeletal healthcare.

To ensure patient access to effective musculoskeletal healthcare treatment options

Page 1

Advocacy for Improvement in Mobility

Thank you.

Sincerely,

Louis F McIntyre, MD
President AIM

**Medication Policy Manual****Policy No:** dru247**Topic:** Orthovisc® (high molecular weight hyaluronan)**Date of Origin:** May 13, 2011**Revised Date:** May 25, 2012**Next Review Date:** May 2013**Effective Date:** May 25, 2012**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

High molecular weight hyaluronan (Orthovisc®) is a substance that is injected directly into the knee joint to help improve the pain associated with osteoarthritis of the knee.

Policy/Criteria

- I. Most contracts require prior authorization approval of high molecular weight hyaluronan prior to coverage. High molecular weight hyaluronan may be considered medically necessary in patients with osteoarthritis of the knee when treatment with hylan G-F 20 (Synvisc[®]/Synvisc-One[®]) OR 1% sodium hyaluronate (Euflexxa[®]) was ineffective or not tolerated.

- II. Administration, Quantity Limitations, and Authorization Period
 - A. Regence does not consider high molecular weight hyaluronan to be a self-administered medication.
 - B. When prior authorization is approved, high molecular weight hyaluronan may be authorized in quantities of up to 2 treatment courses per knee per year for up to one billing unit (30 mg) per claim.
 - C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III. High molecular weight hyaluronan is considered not medically necessary for skin wrinkles or other cosmetic indications.

- IV. High molecular weight hyaluronan is considered investigational when used for all other conditions, including but not limited to osteoarthritis in joints other than the knee.

Position Statement

- Hyaluronic acids are used as viscosupplementation and are injected directly into the knee joint to improve lubrication and reduce the pain associated with osteoarthritis of the knee.
- Hyaluronic acids are generally reserved for use in patients who are not responding to non-pharmacologic therapy (physical therapy, exercise, hot or cold packs) and not responding to or not tolerating simple analgesics such as acetaminophen and NSAIDs.
- There is limited evidence demonstrating that hyaluronic acids are more effective than placebo or non-pharmacologic therapy at increasing mobility and reducing pain associated with osteoarthritis of the knee.
- There is no reliable evidence that any one hyaluronic acid is better or safer than another in the treatment of osteoarthritis of the knee.

- There are inadequate data to determine the benefit of multiple treatment courses of hyaluronic acids.

Clinical Efficacy

- Hyaluronic acids have not been proven in reliable clinical studies to be more effective than non-pharmacologic or generic analgesics such as acetaminophen and NSAIDs.
 - * Systematic reviews of randomized controlled trials evaluating viscosupplementation in patients with osteoarthritis of the knee conclude that there are low quality data available to determine efficacy and safety.^[1,2]
 - * Clinical trials studying the effect of viscosupplementation on knee pain and functional outcomes have reported inconsistent results.
 - * Several studies have reported no improvement in pain or mobility compared to placebo, simple analgesics, or exercise.^[3-6]
- There is no reliable evidence, based on two comparative trials identified, to differentiate between hyaluronic acid products used for viscosupplementation in terms of safety or efficacy.
 - * One randomized controlled trial in 660 patients with osteoarthritis of the knee did not demonstrate a difference in efficacy or safety of Synvisc compared with Orthovisc.^[7]
 - * A randomized trial comparing the effectiveness of Synvisc and Hyalgan is unreliable due to uncertain blinding which may have influenced patient reported outcomes.^[8]
- Hyaluronic acids differ in molecular weight, however there is no reliable evidence to demonstrate that differences in molecular weight impact the safety and efficacy of these medications.^[11]
- Systematic reviews and clinical guidelines have concluded that there is limited evidence to support subsequent treatment courses with hyaluronic acids; however individual patients may benefit from additional courses of hyaluronic acids.^[9,10]
- Hyaluronic acids have been studied in the treatment of osteoarthritis of joints other than the knee, including the hip and the ankle.
 - * Small studies in patients with osteoarthritis of the ankle demonstrated that hyaluronic acid may be an effective treatment option^[11,12]; however, several larger, well-controlled trials have concluded that hyaluronic acid is not effective in this setting (no different than saline).^[13,14]
 - * A randomized trial found hyaluronic acid to be no more effective than placebo in the treatment of osteoarthritis of the hip.^[15]

- The Osteoarthritis Research Society International (OARSI) concludes that hyaluronic acids may be useful in patients with osteoarthritis of the knee; however, they note that there is considerable controversy regarding the cost-effectiveness and the benefit to risk ratio of hyaluronic acids.^[16]
- The American Academy of Orthopaedic Surgeons does not recommend for or against the use of hyaluronic acids for patients with osteoarthritis of the knee.^[17]
- The American College of Rheumatology recommends hyaluronic acids for patients who do not respond to non-pharmacologic therapy and do not respond to or do not tolerate simple oral analgesics.^[9]

Safety

- The most common adverse events reported with hyaluronic acids include joint pain, stiffness and swelling, as well as injection site reactions.^[18-24]
- Adverse reactions are usually mild and improve within a few days. Patients undergoing treatment should avoid strenuous activities (high-impact sports such as jogging, soccer, or tennis) and prolonged weight-bearing activities for approximately 48 hours immediately after an injection.^[18-24]

Dosing Considerations^[18-24]

Hyaluronic Acid	Volume (mg) per dose	Number of Doses per treatment course[†]
Euflexxa (1% sodium hyaluronate)	2 mL (20 mg)	3 doses
Gel-One (sodium hyaluronate)	3 mL (30 mg)	1 dose
Hyalgan (sodium hyaluronate)	2 mL (20 mg)	5 doses*
Orthovisc (high molecular weight hyaluronan)	2 mL (30 mg)	3 - 4 doses
Supartz (sodium hyaluronate)	2.5 mL (25 mg)	5 doses*
Synvisc (hylan G-F 20)	2 mL (16 mg)	3 doses
Synvisc-One (hylan G-F 20)	6 mL (48 mg)	1 dose

[†]All hyaluronic acids are injected once a week

* Some patients have experienced benefit after 3 doses

Cross References
Intra-articular Hyaluronan Injections for Osteoarthritis, BlueCross BlueShield Association Medical Policy, 2.01.31, Issue 08:2010
Maximum Drug Dosage, RegenceRx Medication Policy Manual, Policy No. dru237
Euflexxa [®] , 1% sodium hyaluronate, RegenceRx Medication Policy Manual, Policy No. dru244
Gel-One [®] , sodium hyaluronate, RegenceRx Medication Policy Manual, Policy No. dru275
Hyalgan [®] , sodium hyaluronate, RegenceRx Medication Policy Manual, Policy No. dru245
Supartz [®] , sodium hyaluronate, RegenceRx Medication Policy Manual, Policy No. dru246
Synvisc [®] /Synvisc-One [®] , hylan G-F 20, RegenceRx Medication Policy Manual, Policy No. dru243


Codes	Number	Description
HCPCS	J7323	Hyaluronan or derivative, euflexxa, for intra-articular injection, per dose
HCPCS	J7321	Hyaluronan or derivative, hyalgan or supartz, for intra-articular injection, per dose
HCPCS	J7324	Hyaluronan or derivative, orthovisc, for intra-articular injection, per dose
HCPCS	J7325	Hyaluronan or derivative, synvisc or synvisc-one, for intra-articular injection, 1 mg
HCPCS	J7326	Hyaluronan or derivative, gel-one, for intra-articular injection, per dose
ICD-9	715.16	Osteoarthritis localized primary involving lower leg

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Clinical Policy Bulletin: Viscosupplementation

Number: 0179

Policy

- I. Aetna considers viscosupplementation medically necessary for members with osteoarthritis of the knee who meet all of the following selection criteria:
 - A. Conservative therapy (including physical therapy, pharmacotherapy (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (up to 1 g 4 times/day) and/or topical capsaicin cream)) has been attempted in each joint to be treated with viscosupplements and has not resulted in functional improvement after at least 3 months or the member is unable to tolerate conservative therapy because of adverse side effects; *and*
 - B. The member has documented symptomatic osteoarthritis of the knee; *and*
 - C. The member has failed to adequately respond to aspiration and injection of intra-articular steroids; *and*
 - D. The member reports pain which interferes with functional activities (e.g., ambulation, prolonged standing); *and*
 - E. The pain cannot be attributed to other forms of joint disease; *and*
 - F. There are no contraindications to the injections (e.g., active joint infection, bleeding disorder).

Additional series of injections for members who have responded to previous series are considered medically necessary under the following circumstances:

- A. At least 3 months has elapsed since the prior series of injections; *and*
 - B. The medical record demonstrates a reduction in the dose of NSAIDs (or other analgesics or anti-inflammatory medication) during the 3-month period following the previous series of injections; *and*
 - C. The medical record objectively documents significant improvement in pain and functional capacity as the result of the previous injections.
- II. Aetna considers viscosupplementation experimental and investigational for all other indications such as chondromalacia patellae, facet joint arthropathy, osteochondritis dissecans, or patellofemoral syndrome (patellar knee pain), or for use in joints other than the knee (e.g., ankle, carpo-metacarpal joint, elbow, hip, metatarso-phalangeal joint, shoulder, and temporomandibular joint) because

Policy History

> [Last Review](#): 12/30/2011
 Effective: 11/05/1997
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Viscosupplementation

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the effectiveness of viscosupplementation for these indications has not been established.

- III. Aetna considers intra-articular polynucleotides in the treatment of knee osteoarthritis experimental and investigational because the effectiveness of this approach has not been established.
- IV. Aetna considers viscosupplementation in the treatment of temporomandibular joint disorders experimental and investigational because its effectiveness for this indication has not been established.

Preferred Viscosupplements:

There are several brands of viscosupplements on the market. There is a lack of reliable evidence that any one brand of viscosupplement is superior to other brands for medically necessary indications. Euflexxa (1 % sodium hyaluronate) and Orthovisc (high molecular weight form of hyaluronic acid) brands of viscosupplements ("preferred viscosupplements") are less costly to Aetna. Consequently, because other brands (e.g., Hyalgan (sodium hyaluronate), Supartz (sodium hyaluronate), Synvisc (Hylan G-F 20) and Synvisc One (Hylan G-F 20)) brands of viscosupplements are more costly than these preferred viscosupplements, and preferred viscosupplements are at least as likely to produce equivalent therapeutic results, no other viscosupplements will be considered medically necessary unless the member has a contraindication or intolerance to the two preferred viscosupplements, Euflexxa and Orthovisc.

Background

Osteoarthritis of the knee is a disease in which the elastoviscous properties of the synovial fluid in the knee joint becomes diminished, resulting in less protection and shock absorption. In May 1997, the FDA approved sodium hyaluronate (Hyalgan), an injectable form of hyaluronic acid, for the treatment of pain associated with knee osteoarthritis. In November 1996, the Orthopedics and Rehabilitation Devices Panel of the FDA recommended Synvisc for approval in the United States, with the condition that a post-market study be performed. Hylan G-F 20 (Synvisc and Synvisc One), a cross-linked preparation of hyaluronan, is a viscosupplementation drug injected into knee joints to increase the elastoviscous properties of arthritic joint (synovial) fluid, while at the same time slowing its egress from the joint. Trials have indicated that both compounds appear to result in a small but statistically significant improvement in reducing pain and increasing levels of mobility in the majority of individuals treated, as compared with placebo, and may even slow down deterioration of joints.

Hyalgan is usually given as weekly intra-articular injections administered for up to 5 weeks. Noticeable improvements usually occur beginning at week 5 after treatment initiation, and symptom relief may last for six months. Hyalgan should not be used to treat joint dysfunction.

Two formulations of Hylan GF-20 are currently available. Synvisc is administered once per week for a total of three intra-articular injections. Synvisc One is administered in a single intraarticular injection.

Supartz (sodium hyaluronate) was approved by the FDA on January 24, 2001. It is indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy (e.g., physical

therapy) and simple analgesics (e.g., acetaminophen). Supartz is administered by an injection once a week for a total of five injections.

In 2000, the American College of Rheumatology updated its guidelines for the treatment of OA of the knee. In mild symptomatic OA, treatment may be limited to patient education, physical and occupational therapy and other non-pharmacologic modalities, and pharmacologic therapy including non-opioid oral and topical analgesics. In patients who are unresponsive to this regimen, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is appropriate.

According to ACR guidelines, intra-articular injections of corticosteroids or hyaluronan may be used for patients who fail to respond to management that is more conservative. Patients with severe symptomatic OA of the knee may require surgical intervention, e.g. osteotomy or total joint arthroplasty. The guidelines on knee pain from the American College of Orthopedic Surgeons (1999) and the National Institute for Health and Clinical Excellence (2007) also recommend use of intra-articular steroids in patients with osteoarthritis of the knee that fail to respond to more conservative measures (e.g., NSAIDs or acetaminophen, physical therapy, decreased activity). According to the literature, patients with joint effusions and local tenderness may have greater benefit from intra-articular steroid injections. Neither patient function, radiographic features, intra-articular crystals nor a raised synovial fluid cell count predict a good response (Creamer, 1997). At the basic science level, there are a number of mechanisms by which the improvement is thought to occur - mRNA synthesis, B and T cell function, cytokine levels, metalloproteases and synovial permeability (Creamer 1997, Genovese 1998). The benefits of corticosteroids may also be due to relief of effusions from aspiration and disruption of adhesions within the joint. Although there are only a limited number of studies that have directly compared the viscosupplementation with corticosteroid injections, these studies indicate that corticosteroid injections are as effective as viscosupplementation in the treatment of osteoarthritis of the knee (Johnston, 2003). The most serious complication is septic arthritis, with an incidence of 1/17,000 to 1/50,000 (SCHIN, 2002). There is a risk of local tissue atrophy and depigmentation, particularly when small joints are injected with potent corticosteroids. Concern about progressive joint damage following repeated corticosteroid injections is controversial; despite the large number of people treated with intra-articular corticosteroids, case reports that suggest this may result in joint damage are rare (SCHIN, 2002). According to available literature, it is inadvisable to treat patients with a complete collapse of joint space or bone loss with intra-articular hyaluronic acid or corticosteroids, given their poor clinical response (Evanich, et al., 2001).

Viscosupplementation is a therapeutic modality for the treatment of osteoarthritis based on the physiologic importance of hyaluronan in synovial joints (Bellamy, 2002). Its therapeutic goal is to restore the visco-elasticity of synovial hyaluronan, thereby decreasing pain, improving mobility and restoring the natural protective functions of hyaluronan in the joint. The short-term mode of action of viscosupplementation is believed to be based on the pain relieving effect of the elastoviscous fluid in the affected joint. In the long term, the restoration of the joint mobility due to relief of pain triggers a sequence of events, which restores the trans-synovial flow and subsequently the metabolic and rheological homeostasis of the joint.

According to a review of the literature in the journal *Clinical Evidence* (Scott & Kowalczyk, 2006), compared with placebo, intra-articular hyaluronan and hyaluronan derivatives may improve pain and function compared with placebo at up to 13 weeks after injection, but may have no longer-term benefits. The review stated that this

conclusion is based upon low-quality evidence. The assessment also found that, compared with intra-articular corticosteroids, hyaluronan may be more effective than intra-articular corticosteroids at reducing pain at 5–13 weeks, although they may be as effective as each other in the shorter term. According to the review, this conclusion is based upon very low-quality evidence. The assessment also noted that there is no evidence on the effectiveness of subsequent courses of hyaluronan, and if diminishing returns exist.

Kirwan (1997) reviewed 10 clinical trials of hyaluronan of the knee joint. The review found slightly greater benefit from the injections versus placebo at 1 to 6 months after treatment. Of four subsequently published randomized controlled trials, three (Lohmander, 1996; Corrado, et al, 1995; Formiguera, 1995) found no significant difference versus placebo at 2 to 5 months after treatment, but both active and placebo groups improved compared with baseline. One of the trials (240 people) included a subgroup analysis of people aged over 60 years with moderate to severe symptoms; these benefited more with active treatment than placebo (Lohmander, 1996). The fourth subsequent randomized controlled trial, involving 100 people, found significant benefit on a standardized pain assessment tool (the Lequense index) with hyaluronan versus placebo, both at 5 weeks and four months (Huskisson, 1999). Another randomized controlled clinical trial also found a trend toward greater pain relief and functional recovery in patients treated with intra-articular hyaluronan versus placebo injection, but the differences between the two groups were not statistically significant (Tamir, 2001).

Bellamy (2002) viewed the evidence comparing viscosupplementation to steroid injections. One randomized controlled clinical trial reviewed by Bellamy (2002) found a benefit of hyaluronan at 5 and 8 weeks against steroids, but no difference in effect between steroid and hyaluronan injections was found in two other randomized controlled clinical trials.

The Galacian Agency for Health Technology Assessment (Fernandez Lopez & Ruano-Ravina, 2005) systematically reviewed the evidence for the use of viscosupplementation in hip osteoarthritis. The authors of the systematic review identified seven clinical trials that met the inclusion criteria and one systematic review. The number of patients in the trials ranged from 22 to 104. Five trials had no control group, one compared two viscosupplements of different molecular weight, and the remainder compared viscosupplements with administration of intraarticular glucocorticoids and with a group that received placebo. Relief of pain was estimated to be around 40% to 50% by most studies, though the duration of this effect post-treatment was not known. The authors reported that the randomized clinical trial with three arms reported no differences between the treatments at the end of the follow-up period. Moreover, this study displayed the highest quality of all those included. The authors concluded that the absence of a control group in most of the clinical trials means that there is no way of ascertaining the effectiveness of viscosupplements in hip osteoarthritis. Accordingly, viscosupplements "should not be used outside the ambit of experimental studies until better-quality evidence is available."

In a review on viscosupplementation in the treatment for patients with hip osteoarthritis (OA), Conrozier and Vignon (2005) concluded that to date, in the absence of placebo-controlled studies, the effectiveness of intra-articular injections of hyaluronic acid or its derivatives in the symptomatic treatment of hip OA cannot be determined conclusively. Nevertheless the published data suggest that viscosupplementation may be effective. These researchers stated that double-blind, controlled studies are needed to confirm

these data, before viscosupplementation should be included into the treatment paradigm for patients with hip OA.

Migliore, et al. (2006) reported the effects of hylan G-F 20 administered through ultrasound (US)-guided intra-articular (IA) injections in patients with symptomatic hip OA. They treated 30 patients with symptomatic hip OA. Under US guidance, 7 patients received one injection, 21 patients had two injections, and 2 patients received three injections, each with 2 ml of hylan G-F 20. Lequesne index, visual analog scale (VAS) scale of hip pain, and NSAID consumption were evaluated at baseline as well as 2 and 6 months after the beginning of the treatment. No systemic adverse events were observed. Lequesne index, VAS pain score, and NSAID consumption showed a reduction that was statistically significant to the baseline. The present observation suggested the potentiality for the safety and effectiveness of hylan G-F 20 injected under US guidance in patients with symptomatic hip OA. The authors stated that further controlled studies are needed.

The Canadian Agency for Drugs and Technologies in Health's report on IA hyaluronic acid for hip OA (Dagenais, 2007) stated that the best available evidence suggests that hyaluronic acid may offer symptomatic relief in patients with mild to moderate hip OA for whom other conservative therapies are contraindicated or have failed. Currently, there is insufficient good quality evidence to determine this conclusively.

van den Bekerom, et al. (2006) evaluated the effectiveness of viscosupplementation in the treatment of hip OA. A total of 16 articles concerning the effectiveness of a total of 509 patients undergoing viscosupplementation for hip OA were included – 12 European studies, 3 Turkish studies and 1 American study with levels of evidence ranging from I to IV evaluated the following products: Hylan G-F 20, Hyalgan, Ostenil, Durolane, Fermatron and Orthovisc. Heterogeneity of included studies did not allow pooled analysis of data. The authors noted that despite the relatively low level of evidence of the included studies, viscosupplementation performed under fluoroscopic or ultrasound guidance seems an effective treatment and may be an alternative treatment of hip OA. Intra-articular injection of (derivatives of) hyaluronan (HA) into the hip joint appears to be safe and well-tolerated. However, the authors stated that viscosupplementation can not be recommended as standard therapy in hip OA for wider populations, and therefore the indications remain a highly individualized matter.

In a pilot study, Salk, et al. (2005) examined the safety and effectiveness of viscosupplementation with sodium hyaluronate versus phosphate-buffered saline control for pain associated with OA of the ankle. Results of this study suggested that 5 weekly intra-articular injections of sodium hyaluronate in patients who have OA of the ankle are well tolerated, can provide sustained relief of pain, and improve ankle function. These findings are consistent with previously published studies using intra-articular injections of sodium hyaluronate in other articular joints but require confirmation in a large, randomized, saline-controlled study. These investigators concluded that if confirmed, these findings would provide a valuable non-operative treatment option for patients who have OA of the ankle.

Carpenter and Motley (2008) noted that although anecdotal data exist, no long-term studies regarding the use of viscosupplementation in the ankle have been published to date. These researchers compared pain reduction following ankle arthroscopy versus that following ankle arthroscopy combined with weekly intra-articular instillation of hylan G-F 20 during the first 3 post-operative weeks. They found that both treatment groups experienced statistically significantly decreased pain following the intervention ($p = 0.002$ and $p = 0.0009$ for the arthroscopy alone and arthroscopy plus hylan groups,

respectively), and that those who received 3 intra-articular injections of hylan G-F 20 following ankle arthroscopy improved statistically significantly ($p = 0.0014$) more than did those who underwent arthroscopy as a sole therapy. These preliminary results suggested that viscosupplementation combined with arthroscopy may be more beneficial than arthroscopy alone, and provide further insight into the role of viscosupplementation in the treatment of ankle OA.

van Brakel and Eygendaal (2006) assessed the safety and effectiveness of IA injection of hyaluronic acid in 19 consecutive elbows with post-traumatic OA. In 18 patients (10 male and 8 female patients; mean age, 45.6 years [SD, 15.0 years]), 3 injections of sodium hyaluronate were given within 4 weeks at regular intervals. Evaluation took place just before the first injection, as well as after 3 and 6 months, and consisted of the Elbow Function Assessment Score, the Functional Rating Index of Broberg and Morrey, and the Modified Andrews Elbow Scoring System. Pain was also assessed by means of VAS. Viscosupplementation resulted in slight, short-term pain relief and a very limited decrease in activity impairment at evaluation after 3 months. After 6 months, no beneficial effects were noticed in any of the 19 injected elbows. Other parameters were not influenced by treatment with viscosupplementation at any time. Systemic or local adverse effects did not occur. The authors concluded that because the use of viscosupplementation for the treatment of post-traumatic OA of the elbow provides only slight, short-term pain relief and a very limited decrease in activity impairment and the other parameters were not modified, viscosupplementation is not suitable for this indication.

An assessment of viscosupplementation for knee osteoarthritis by the Canadian Agency for Drugs and Technologies in Health (CADTH) (Dagenais, 2006) found that evidence suggests modest short-term reductions in pain and improvements in function, and no superiority among viscosupplement products. Adverse events are rare, benign, temporary, and likely associated with the intraarticular injection. The assessment reported that clinical practice guidelines and evidence suggest that this approach is most suitable for patients with mild to moderate knee osteoarthritis, and in those for whom other approaches are contraindicated, or have failed.

Guidance from the National Institute for Health and Clinical Excellence (2008) found that the research evidence on the efficacy of viscosupplementation is often difficult to interpret because of confounders including different molecular weights of hyaluronans, different injection schedules (ranging from once weekly to a series of 5 injections), poor trial design despite large numbers of studies (for example lack of intention-to-treat analyses, limitations in blinding). The guidance concludes that the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of 3-5 injections, although the effect size is generally small. "Given this, and the cost of the therapies together with increased clinician visits required for injections, there appears to be a poor rationale for routine clinical use." The guidance noted that clinical trials do not suggest subgroups of osteoarthritis patients who may have greater benefit from viscosupplementation.

An assessment by AETMIS (2007) reached similar conclusions to the NICE guidance. The AETMIS assessment concluded that viscosupplementation offers clinically modest relief from the symptoms of knee osteoarthritis over a period that could last up to several weeks. The assessment found viscosupplementation to be a safe short-term treatment. The assessment noted, however, that these conclusions are based on secondary analyses of a multitude of small primary studies of poor methodological quality. AETMIS reported that available data did not help distinguish differences in the

effectiveness of any one product over the others. They were also unable to identify patient subgroups more likely to benefit from this treatment compared with other available therapeutic modalities. AETMIS concluded that, given the modest effectiveness of viscosupplementation compared with its relatively high cost and the additional professional resources required to administer it, it is not currently justified to contemplate funding viscosupplementation for all patients with osteoarthritis of the knee. The assessment noted, however, that it is possible that viscosupplementation could be offered as a last-resort treatment to patients who do not achieve pain relief from conventional therapies or for whom these are contraindicated.

A systematic evidence review prepared by the BlueCross BlueShield Association Technology Evaluation Center Evidence-based Practice Center for the Agency for Healthcare Research and Quality (Samson, et al., 2007) concluded:

"Viscosupplementation trials generally report positive effects on pain and function scores compared to placebo, but the evidence on clinical benefit is uncertain, due to variable trial quality, potential publication bias, and unclear clinical significance of the changes reported."

The American Academy of Orthopaedic Surgeons' clinical guideline on the treatment of OA of the knee (2008) can not recommend for or against use of intra-articular HA injections.

There is limited evidence of the effectiveness of repeat viscosupplement treatments. Available evidence is limited to uncontrolled case series, so that improvements following repeat treatment may be due to the natural history of the condition and placebo effects. Evidence submitted to the FDA regarding repeat treatment consisted of two studies. One study, by Scali, et al. (1995) was an uncontrolled study of 5 weekly injections of viscosupplementation repeated every 6 months for 30 months, for a total of 25 injections. A second study by Kotz and Kolarz (1999) examined the effectiveness of viscosupplementation in 108 patients, 14 of whom received repeat injections within 4 to 8 months due to pain recurrence, 6 of whom completed 12 month followup. Guidance from the National Institute for Health and Clinical Excellence (NICE, 2007) found that the evidence seems to suggest a benefit for reducing pain up to 3 months after a series of 3-5 injections, although the effect size is generally small.

In a randomized controlled trial, Jüni, et al. (2007) compared the safety and effectiveness of intra-articular hylan and two hyaluronic acids (HAs) in OA of the knee (n = 660). Patients were randomly assigned to receive 1 cycle of 3 intra-articular injections per knee of 1 of 3 preparations: (i) a high molecular weight cross-linked hylan, (ii) a non-cross-linked medium molecular weight HA of avian origin, or (iii) a non-cross-linked low molecular weight HA of bacterial origin. The primary outcome measure was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score at 6 months. Secondary outcome measures included local adverse events (effusions or flares) in injected knees. During months 7 to 12, patients were offered a second cycle of viscosupplementation. Pain relief was similar in all 3 groups. The difference in changes between baseline and 6 months between hylan and the combined HAs was 0.1 on the WOMAC pain score (95% confidence interval [95% CI] -0.2, 0.3). No relevant differences were observed in any of the secondary efficacy outcomes, and stratified analyses provided no evidence for differences in effects across different patient groups. There was a trend toward more local adverse events in the hylan group than in the HA groups during the first cycle (difference 2.2% [95% CI -2.4, 6.7]), and this trend became more pronounced during the second cycle (difference 6.4% [95% CI 0.6, 12.2]). The authors concluded that there was no evidence for a difference

in effectiveness between hylan and HAs. In view of its higher costs and potential for more local adverse events, these investigators see no rationale for the continued use of hylan in patients with knee OA.

In a pilot study, Cleary and colleagues (2008) examined the potential effectiveness of HA injection therapy in the treatment of lumbar facet joint arthritis. A total of 13 patients with symptomatic lumbar facet joint arthritis who met the inclusion criteria were prospectively recruited. Pre-treatment evaluation of patients was by questionnaire, including the VAS and Oswestry Disability Questionnaire. A single injection of HA into affected facet joints was then performed, with correct placement confirmed on fluoroscopy. Patients were similarly evaluated 6 weeks after treatment. A total of 18 facets were injected with HA. At 6-week follow-up, there was no significant improvement in pain when measured on the VAS. There was also no significant improvement in the Oswestry Disability Questionnaire. The authors concluded that preliminary results from this pilot study did not demonstrate any benefit of viscosupplementation in the management of symptomatic lumbar facet joint arthropathy.

Grogan and colleagues (2009) noted that in the recent past, non-surgical treatment of OA was limited to rest, immobilization, physical therapy, activity modifications, NSAIDs, analgesics, weight loss, assistive devices for walking, and corticosteroid injections. Viscosupplementation is a welcome addition to the non-surgical armamentarium available to physicians. It is used to introduce hyaluronic acid into the joint to provide initial lubrication and shock absorption, and to change the long-term disease process. These investigators discussed the pathology of OA; the characteristics, physiology, and administration of commercial viscosupplements; and reviewed the research on hyaluronic acid (HA) use in the foot and ankle. They concluded that additional studies are needed to test the safety and effectiveness of this treatment in other parts of the foot. Furthermore, in a review on the use of HA as a treatment for ankle OA, Sun, et al. (2009) stated that there is only limited published literature relating to the use of HA in the ankle.

Salini, et al. (2009) evaluated the effectiveness of a single ultrasound-guided injection of HA in patients suffering from carpo-metacarpal OA (CMC-OA). A total of 18 patients with CMC-OA, grade 2-3 Kellgren and Lawrence score were enrolled. They underwent clinical evaluation at baseline and after 1 month follow-up, evaluating: grading of pain (VAS at rest and during activities), function (Dreiser Index), grip and pinch strengths (Jamar dynamometer), as well as NSAIDs consumption. Each patient received a single ultrasound-guided injection of HA into the articular CMC joint. The results were that pain at rest and during activities decreased from 1.8 +/- 1.07 to 0.5 +/- 0.68 ($p < 0.001$) and from 8.05 +/- 0.94 to 4.15 +/- 1.42 ($p < 0.001$), respectively. Dreiser Functional Index showed a significant improvement (+11.59%; $p < 0.004$), as well as pulp pinch strength (24.07%; $p < 0.001$). The consumption of NSAIDs was also clearly reduced, from 16 to 7 patients (-45%) and from 2.45 +/- 1.98 to 1.15 +/- 1.30 tablets per week ($p < 0.02$). Mild local side effects, lasting less than 3 hours, were observed only in 2 cases. The authors concluded that a single ultrasound-guided injection of HA is a safe and effective procedure in CMC-OA, with a significant improvement in terms of pain and function. However, they stated that studies with larger samples and longer term follow-up are needed.

Conrozier, et al. (2009) assessed the effectiveness and tolerability of a single intra-articular injection of non-animal-stabilized HA (NASHA) in patients treated for symptomatic hip OA (HOA). A total of 40 patients suffering from HOA were treated by a single intra-articular injection of NASHA in the painful hip under fluoroscopy. Patient

global assessment (PGA) and walking pain (WP) on a 100-mm VAS, WOMAC index, and Lequesne index were assessed at each visit. Treatment effectiveness was assessed using OMERACT-OARSI response criteria, minimal clinically important improvement (MCII), patient acceptable symptom state (PASS) obtained from PGA, WOMAC and WP. Predictive factors of effectiveness were also studied. A total of 34 patients were assessable (mean follow-up of 159 days). All clinical variables (WP, PGA, WOMAC, Lequesne index) decreased significantly between baseline and last evaluation. Twenty-two patients (71%) were classified OMERACT-OARSI responders, 25 subjects (75.8%) were classified PASS+, and 19 (61.3%) fulfilled criteria for MCII. Out of clinical and radiological variables only Lequesne index ($p = 0.04$) and WOMAC ($p = 0.04$) at baseline were found to be predictive of treatment effectiveness; the treatment was well-tolerated. There were no severe adverse events related to the treatment or to the procedure. However 15 of the 28 assessable patients experienced transient increase of pain in the target hip during the first week following injection. The authors concluded that viscosupplementation of the hip with NASHA is easily feasible in daily clinical practice, safe and well-tolerated despite a frequent increase of pain the days following injection. Moreover, they stated that prospective, controlled trials are needed to confirm these data and to evaluate both safety and effectiveness of a second course of treatment.

The American Academy of Orthopedic Surgeons published a clinical practice guideline on the treatment of glenohumeral osteoarthritis in the adult patient population (Izquierdo et al, 2010). Of the 16 recommendations addressed, 9 are inconclusive. Two were reached by consensus -- that physicians use peri-operative mechanical and/or chemical venous thromboembolism prophylaxis for shoulder arthroplasty patients and that total shoulder arthroplasty not be performed in patients with glenohumeral osteoarthritis who have an irreparable rotator cuff tear. Four options were graded as weak: (i) the use of injectable viscosupplementation; (ii) total shoulder arthroplasty and hemiarthroplasty as treatment; (iii) avoiding shoulder arthroplasty by surgeons who perform fewer than 2 shoulder arthroplasties per year (to reduce the risk of immediate post-operative complications); and (iv) the use of keeled or pegged all-polyethylene cemented glenoid components. The single moderate-rated recommendation was for the use of total shoulder arthroplasty rather than hemiarthroplasty. The clinical guideline noted that management of glenohumeral osteoarthritis remains controversial; the scientific evidence on this topic can be significantly improved.

In a randomized, double-blind clinical trial, Vanelli and associates (2010) evaluated the safety and effectiveness of intra-articular polynucleotides (PN) gel injections in the treatment of knee OA associated with persistent knee pain. A total of 60 patients were enrolled and randomized to receive intra-articular polynucleotides ($n = 30$) or hyaluronan ($n = 30$); patients received 5 weekly intra-articular knee injections and the follow-up period was 3 months after the end of treatment. Primary endpoint was to determine PN efficacy in reducing knee pain at the end of the study over baseline value and over standard HA viscosupplementation. Pain levels were measured using a 0 to 10 cm VAS. Secondary endpoints included knee osteoarthritis outcome score (KOOS), NSAIDs consumption, crackling during movement and articular mobility limitation. The mean global VAS pain decreased from 5.7 ± 1.9 cm (T0) to 1.9 ± 1.5 cm (T16) in the PN group and from 4.8 ± 2.0 cm (T0) to 2.1 ± 1.4 cm (T16) in the HA group. The reduction in pain was statistically significant for both groups. Increases of KOOS from baseline values were statistically significant in both groups. No significant adverse events were reported. The authors concluded that these findings suggest that intra-articular PN can be a valid alternative to traditional HA supplementation for the

treatment of knee OA. These preliminary findings need to be validated by further research.

In a systematic review, Manfredini and colleagues (2010) examined the clinical studies on the use of HA injections to treat temporomandibular joint (TMJ) disorders performed over the last decade. The selected papers were assessed according to a structured reading of articles format, which provided that the study design was methodologically evaluated in relation to 4 main issues: (i) population, (ii) intervention, (iii) comparison, and (iv) outcome. A total of 19 papers were selected for inclusion in the review, 12 dealt with the use of HA in TMJ disk displacements and 7 dealt with inflammatory-degenerative disorders. Only 9 groups of researchers were involved in the studies, and less than half of the studies (8/19) were randomized and controlled trials. All studies reported a decrease in pain levels independently by the patients' disorder and by the adopted injection protocol. Positive outcomes were maintained over the follow-up period, which ranged between 15 days and 24 months. The superiority of HA injections was shown only against placebo saline injections, but outcomes are comparable with those achieved with corticosteroid injections or oral appliances. The available literature seems to be inconclusive as to the effectiveness of HA injections with respect to other therapeutic modalities in treating TMJ disorders. The authors concluded that studies with a better methodological design are needed to gain better insight into this issue and to draw clinically useful information on the most suitable protocols for each different TMJ disorder.

Appendix

Table: Viscosupplementation Dosing

Drug	Dose
Euflexxa (1% sodium hyaluronate)	20 mg once a week (1 week apart) for a total of 3 injections.
Hyalgan (sodium hyaluronate)	20 mg once a week (1 week apart) for a total of 5 injections.
Orthovisc (high molecular weight hyaluronan)	30 mg once a week (1 week apart) for a total of 3 - 4 injections.
Supartz (sodium hyaluronate)	10 mg once a week (1 week apart) for a total of 5 injections.
Synvisc One (Hylan G-F 20)	48 mg one time injection.
Synvisc (Hylan G-F 20)	16 mg once a week (1 week apart) for a total of 3 injections.

Sources: Euflexxa prescribing information; Hyalgan prescribing information; Orthovisc prescribing information; Supartz prescribing information; Synvisc One prescribing information; Synvisc prescribing information.

CPT Codes / HCPCS Codes / ICD-9 Codes

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CPT codes covered if selection criteria are met

20610

CPT codes not covered for indications listed in the CPB:

20600

20605

HCPCS codes covered if selection criteria are met

J7321	Hyaluronan or derivative, Hyalgan or Supartz, for intra-articular injection, per dose [knee only - see selection criteria]
J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose [knee only - see selection criteria] [Aetna preferred brand]
J7324	Hyaluronan or derivative, Orthovisc, for intra-articular injection, per dose [knee only - see selection criteria] [Aetna preferred brand]
J7325	Hyaluronan or derivative, Synvisc, or Synvisc-One for intra-articular injection, 1 mg [knee only - see selection criteria]
J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose

ICD-9 codes covered if selection criteria are met:

715.18	Osteoarthritis, localized, primary, lower leg [knee only - see selection criteria]
715.26	Osteoarthritis, localized, secondary, lower leg [knee only - see selection criteria]
715.36	Osteoarthritis, localized, not specific whether primary or secondary, lower leg [knee only - see selection criteria]
715.96	Osteoarthritis, unspecified whether generalized or localized, lower leg [knee only - see selection criteria]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive)

524.60 - 524.69	Temporomandibular joint disorders
715.00 - 715.15, 715.17 - 715.25, 715.27 - 715.35, 715.37 - 715.95, 715.97 - 715.98	Osteoarthritis and allied disorders [joints other than knee]
717.7	Chondromalacia of patella [chondromalacia patellae]

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719.46 Pain in joint, lower leg [patellofemoral syndrome]

732.7 Osteochondritis dissecans

ICD-9 codes contraindicated for this CPB (not all-inclusive)

286.0 - 286.9 Coagulation defects [bleeding disorder]

711.00 - Arthropathy associated with infections [active joint infection]
711.99**The above policy is based on the following references:**

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1/12/2012

Masters, Christine V. (HCA)

From: Rugo, Eric <eric.rugo@stryker.com>
Sent: Wednesday, December 12, 2012 6:23 AM
To: Masters, Christine V. (HCA)
Subject: RE: HTA Program Update: Selected Technologies Public Comment Period

Follow Up Flag: Follow up
Flag Status: Completed

Hello Christine, I want to draw your attention to the re-review of HA injections. This is a technology that I think WA has evaluated more than once (not sure though). Also on balance, this is not a product we sell and is not a race we have a horse in. I bring it up because I get concerned that revisions to the this assessment sooner or later they will spin it to say what they want to hear. That said, if the clinical lit on this product was insufficient and there is now a great RCT that is believed to fill the gaps in the existing data, I can see the possible reasonableness of opening an assessment up again. Do the regs governing this control how this works... Thoughts...



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From: Steven St. George, Sr. Manager, Market Access and US Reimbursement
Phone: 952-830-6364
E-mail: steven.stgeorge@zimmer.com
Date: 08.04.2013
Subject: Regarding Proposed Washington HTA re-review of Hyaluronic Acid/Viscosupplementation

Dear Mr. Stevenson:

Thank you for the opportunity to comment on the Draft Key Questions for the re-review of Hyaluronic Acid / Viscosupplementation.

Our comments regarding the questions are brief, however, we also recommend the inclusion of an additional question that we believe will help clarify the important place that Hyaluronic Acid/Viscosupplementation plays in the continuum of treatment for pain associated with osteoarthritis of the knee. Suggested edits are highlighted in red below.

*1a: What is the clinical effectiveness of viscosupplementation for treatment of **pain associated with OA** of the knee?*

We agree that this is an appropriate question however we feel it is important to clarify that HA/Viscosupplementation is a treatment of pain associated with OA of the knee, not a treatment for OA.

1b: Do different viscosupplementation products vary in effectiveness?

We agree with this question.

*2. What are the adverse effects associated with viscosupplementation in patients with OA of the knee **compared with alternative treatments**?*

We agree with this question, however, comparisons with other knee osteoarthritis treatments should be highlighted. These should be categorized based on risk levels and should include mortality and morbidity rates. For example there are well documented NSAID safety issues.

*3. Does the effectiveness of viscosupplementation vary by subpopulation defined by these factors: **age, race/ethnicity, gender, primary versus secondary OA, disease severity and duration, weight (body mass index), and prior treatments**?*

We agree with this question.

*4. What are the cost implications and cost-effectiveness of **treatment options for pain associated with OA**?*

We agree with this question, however, cost-effectiveness should appropriately be looked at through the same lens as other pain medications. That is, HA/Viscosupplements are indicated specifically for reducing pain and therefore should be measured vs. NSAIDs, opioids, etc.

Proposed new question:

*5. In the hypothetical absence of Hyaluronic Acid/Viscosupplement therapy, what **safe and effective evidence-based alternative therapies** are available?*

Again, thank you for the opportunity to comment on the Draft Key Questions.