

Hyaluronic Acid / Viscosupplementation

Draft Evidence Report: Public Comment & Response

October 14, 2013

Health Technology Assessment Program (HTA)

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Hyaluronic Acid/Viscosupplementation

Response to Draft Report

October 14, 2013

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Response to Public Comments, Draft Report***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.

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cite evidence, the information is forwarded to the vendor for consideration in the evidence report.

This document responds to comments from the following parties:

- Bioventus: Peter Heeckt, MD, PhD; Chief Medical Officer
- Vinod Dasa, MD; Associate Professor, Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana
- DePuy Mitek, Inc.: Brad Bisson, Samir Bhattacharyya, Julia Hwang, Brooks Story, and Suresh Aravind
- Ferring Pharmaceuticals, Inc.: Faizan M. Niazi, PharmD; Associate Medical Director, Orthopaedics
- Hyaluronic Acid/Viscosupplementation Coalition (submitted by Ken Long on behalf of Bioventus, DePuy Synthes Mitek sports Medicine, Ferring, Fidia, and Zimmer)
- Zimmer, Inc.: Yvonne Bokelman, MBA, FACH, Senior Director, Global Market Access, Health Economics & Reimbursement

Table 1 provides a summary of comments with responses. NOTE: Comment submissions were considered in no particular order but responses are presented in alphabetical order.

Table 1. Public Comments on Draft Report, Hyaluronic Acid/Viscosupplementation

Key: AAOS, American Association of Orthopaedic Surgeons; HA, hyaluronic acid or hyaluronan; IA, intra-articular; MCID(I), minimal clinically important difference(improvement); NSAID, nonsteroidal anti-inflammatory agent; OA, osteoarthritis; PICO, populations-interventions-comparators-outcomes; QALY, quality-adjusted life-year; QOL, quality of life; RR, relative risk; TKA, total knee arthroplasty; VS, Viscosupplementation

Comment and Source	Response
September 4, 2013 Letter from Peter Heeckt, MD, PhD, Bioventus	
<p>“Viscosupplementation . . . is a cost effective OA treatment, vital as an alternative to surgical interventions, is a critically important option for patients with GI or CV comorbidities for whom chronic NSAID administration is contraindicated, and for patients who are not good candidates for total knee replacement (TKR). In clinical practice, the goal of treatment with viscosupplementation is, often in parallel with other treatments, to treat pain and to increase function.”</p>	<p>Thank you for this perspective.</p>
<p>The commenter objects to the inclusion of non-FDA-approved products in the analysis by Rutjes et al. (2012) and in the 2013 AAOS guidelines.</p>	<p>Please see responses in this document to other comments on this issue.</p>
<p>The commenter raises the issue of saline injection as an active treatment.</p>	<p>Please see responses in this document to other comments on this issue.</p>
<p>“Conclusions based on calculations of effectiveness of IAHA on performance vs. saline injections, without consideration of baseline improvement, are not valid indicators of efficacy. This is especially true when calculating minimal clinical important improvement (MCII). In practice, MCII should be a measure of the patient reported improvement from baseline. Both Rutjes and AAOS</p>	<p>Please see responses in this document to other comments on this issue.</p>

Comment and Source	Response
<p>inappropriately measured MCII as a group mean delta between saline and IAHA.”</p>	
<p>The commenter objects to the inclusion of “non-peer reviewed sources including ‘content experts’, ‘conference proceedings’, ‘review articles’ and clinical trial registries’.”</p>	<p>It is Hayes’ impression that content experts, review articles, and clinical trial registries were consulted by Rutjes et al. only as sources that could identify clinical studies. Please see responses in this document to other comments about the inclusion of unpublished studies and conference abstracts in the Rutjes analysis.</p>
<p>The commenter summarizes findings from a meta-analysis of comparator trials, comparing viscosupplementation with intraarticular corticosteroid injections, and refers to an AAOS guideline recommendation that “Injections of IA hyaluronate may be useful in patients with knee or hip OA. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids.”</p>	<p>Presumably, the commenter is referring to the meta-analysis by Bannuru et al. (2009), which is reviewed in the report. The report acknowledges the comparative advantages and disadvantages of the 2 types of injection.</p>
<p>“There is a profound safety difference between IA-HA and IACS, related to their fundamentally different mechanism of action. Corticosteroids are potent anti-inflammatory drugs, and as such can depress immune function and shift tissue metabolism. Corticosteroid injections must be used cautiously because of their multiple drug interactions (aspirin, anticoagulants, diuretics, estrogen, phenytoin, rifampin, phenobarbital, macrolide antibiotics/antifungals such as erythromycin, ketoconazole, and diabetes drugs) and their contraindication in patients with many types of comorbidities (hypersensitivity, pituitary or adrenal hypofunction, osteoporosis, infection, compromised immune system, etc.) Contraindications to intra-articular glucocorticoid injection include infection in or around the joint, bacteremia or</p>	<p>Thank you for this biological and clinical perspective. Unfortunately, no studies or meta-analyses comparing the incidence and severity of adverse events between the 2 types of injections were identified in the literature.</p>

Comment and Source	Response
<p>sepsis, significant skin breakdown at the injection site, osteochondral or other intra-articular fracture at the joint to be injected, and severe joint destruction¹⁰. Other, uncommon potential side effects of intra-articular glucocorticoid treatment include tendon weakening and rupture, fat and skin atrophy, and muscle wasting precipitated by misdirected injections; nerve and blood vessel damage, due to misdirected injections; steroid arthropathy; and systemic effects caused by high doses and simultaneous injection of multiple joints. Post-injection flares can also occur in about 2% to 6% of patients and are believed to result from chemical synovitis in response to the injected crystals. According to one author, and often recommended in practice, after a corticosteroid injection in the knee, the patient should remain in bed or at rest and avoid walking as much as possible for 3 days, and then use crutches or cane for the next 2 to 3 weeks. “</p>	
<p>The commenter refers to the gastrointestinal and cardiovascular effects of NSAIDs and points out that since the Vioxx and Bextra recall NSAID manufacturers have been required “to revise the labeling (package insert) for their products to include a <u>boxed warning</u>, highlighting the potential for increased risk of cardiovascular events and the well described, serious, potential life-threatening gastrointestinal bleeding associated with their use. No such warnings are needed for IA-HA products.”</p>	<p>The comparative safety of NSAIDs and HA injections is discussed in the report.</p>
<p>“Please note the following quote from the 2013 AAOS Guideline on Treatment of OA of the Knee, ‘We base evidence grades on the quality and applicability ratings, <u>whether or not the studies report critical outcomes, and potential harm to patients.</u>’ As such, it is highly important to note that in the development of the AAOS</p>	<p>Thank you for this observation. Hayes agrees that comparative safety was not explicitly considered in the AAOS recommendation regarding HA injection and the report’s characterization of the AAOS recommendation has been modified accordingly.</p>

Comment and Source	Response
<p>Guidelines in 2013, there was no evaluation or consideration of safety. As such, an effective, yet dangerous treatment such as NSAIDs received a positive recommendation from the society.”</p>	
<p>“Lastly we wish to bring to your attention the fact that Viscosupplements are a covered benefit by Medicare AND by every private insurance carrier in the state of Washington. A decision to cease coverage for those receiving state benefits will serve to single out and dis-advantage this patient population. “</p>	<p>Thank you for this perspective.</p>
<p>September 4, 2013 e-mail from Vinod Dasa, MD, Louisiana State University Health Sciences Center</p>	
<p>“Rutjes et al. and AAOS included non FDA HA products in their analysis. There is likely a reason many products around the world have not been approved by the FDA, because they did not demonstrate adequate safety of efficacy.”</p>	<p>Of the 18 largest trials (100 patients in each arm) included in the main Rutjes analysis, 15 trials used FDA-approved products. The other 3 larger trials were conducted in Canada and Europe and are assumed to have used products subject to the marketing regulations of those regions.</p>
<p>“The AAOS guidelines only gave positive recommendations to 3 treatments (weight loss, NSAID’s, and exercise). They were also unable to demonstrate pain relief with narcotics or steroid injections for arthritic knee pain (both inconclusive) which are both the mainstays of treatment for millions of patients. This makes very little clinical sense given the experience of millions of patients and physicians.”</p>	<p>An analysis of the AAOS recommendations on treatments other than HA injection is beyond the scope of this report. However, the report does include commentary on pain treatments other than HA injection.</p>
<p>“Many of the publications used in the various meta analyses were methodologically flawed. One example is inclusion of patients w bone on bone OA. It has been well studies [sic] that patient w severe OA will not benefit from HA injections. Thus it’s no wonder effect size compared to saline in some trials was minimal. How can one expect a patient w bone on bone OA to receive any relief with</p>	<p>In the study groups of the 21 trials reviewed for this report that had sample sizes ≥ 200 (and thus the greatest influence on pooled estimates), the most severe cases of OA were Kellgren-Lawrence grade III osteoarthritis, i.e., not bone on bone, in all but 4 studies and in those 4 studies, only some patients had Kellgren-Lawrence grade IV or Albäck grade II</p>

Comment and Source	Response
<p>HA when the only treatment that will work is a knee replacement?"</p>	<p>disease.</p>
<p>"Rutjes et al included non peer reviewed or non published information such as as brochures, emails, conference proceedings... how can one possibly analyze information from this low quality evidence?"</p>	<p>As shown in Appendix V of the report, unpublished studies accounted for only 5 of the 71 comparisons represented in the main Rutjes analysis and thus had little effect on the overall pooled estimate. Conference proceedings accounted for another 14 comparisons, but the pooled estimate for conference proceedings was larger (SMD, -0.63) than the pooled estimate for fully published journals (SMD, -0.36); thus, inclusion of conference proceedings served to increase rather than decrease the overall estimate.</p>
<p>"2 authors reviewed in the rutjes et al review , Mcalindon et al and Navarro et al, have submitted letters to the editor questioning rutjes et al's interpretation of their data."</p>	<p>No study by McAlindon et al. was mentioned in the Rutjes review. Numerous critiques of the Rutjes review appear in other comments and are addressed in this document or in the report.</p>
<p>"The serious AE inference in the Rutjes et al is without any clinical merit. From a regulatory perspective the FDA has not recalled or found any reason to question the safety of any US approved HA injections. From a biologic perspective, there is no plausible explanation based on current medical knowledge for HA injections to cause an AE such as cancer. This statement by Rutjes et al is sensationalistic w no biologic foundation. OF the millions of injections given worldwide, why is this the first ever recognition of these serious AE's? Have these AE's managed to escape the view of all the regulatory agencies worldwide (including FDA), corporations, physicians, registries, specialty societies, and patients for over 20 years? This alone may call into question the motives and validity of Rutjes et al."</p>	<p>This issue was discussed in the report.</p>

Comment and Source	Response
<p>“There have been many statistical debates and questions around the continuous reanalysis of various analyses which has become mind numbing to the point where the average physician can no understand what is reality.”</p>	<p>The most comprehensive analyses have suggested very similar conclusions.</p>
<p>“The current paradigm of NSAID’s and steroid injections create additional cost from their medical complications especially when compared to HA injections which are not accounted for in reviews such as this.”</p> <p>“Nsaid’s and narcotics are not the answer to OA treatment and will only increase harm and cost. Decisions that eliminate safe alternatives such as HA injections will invariably lead to increased surgery and in turn undermine an important objective of the current healthcare climate which is to create value and control cost.”</p>	<p>All available clinical studies and cost-effectiveness studies comparing HA with NSAIDs or with usual care that includes NSAIDs are reviewed in the report. The report acknowledges evidence from several sources showing HA to be associated with a reduced rate of GI complications.</p>
<p>“HA injections from a basic science perspective have been found to be chondroprotective which is very important if we are trying to lower the arthroplasty burden.”</p>	<p>This is acknowledged in the Background section.</p>
<p>“Patients w mild to moderate OA do benefit from HA injections whereas patients with bone on bone OA will not benefit.”</p>	<p>Evidence presented in response to Key Question #3 includes findings suggesting that less severe OA is associated with better outcomes from HA injection.</p>
<p>September 4, 2013 Letter from Faizan M. Niazi, Ferring</p>	

Comment and Source	Response
<p>“We maintain our position that viscosupplementation with HA is an effective and safe option for patients unable to achieve adequate pain relief with other interventions or who cannot tolerate adverse events associated with acetaminophen, non-steroidal anti-inflammatory drugs, or corticosteroid injections, or those who are unwilling to accept the well-known risks associated with these drugs. I hope that this safe and effective option will not be denied to the state employees.”</p>	<p>Thank you for your comment.</p>
<p>“A primary concern of the analysis by Rutjes et al, is that it consist of US and non-US products. Of the 15 products included in the analysis, only six of were FDA approved. We cannot be certain if non FDA approved products would meet the current safety, efficacy and manufacturing standards required for here in the US. Due to the inclusion of ex-US products, the applicability of this analysis to the US population comes into question. It is clear that there are many differences in the sourcing of products (avian or bacterial), molecular weight, structural and purification processes.”</p>	<p>No analyses of the comparative effectiveness of products with and without FDA approval have been published. Published analyses of differential effectiveness according to chemical structure and molecular weight have failed to show a difference.</p>
<p>“nearly a third of the data incorporated were not from peer reviewed full print journals including content experts, poster presentations, review articles, and clinical trial registries. The inability to disclose the contributory data calls into question the transparency of the analysis.”</p>	<p>In stratified analysis, the effect size across conference abstracts was actually larger than the effect size across fully published studies, and the number of totally unpublished studies was too small to appreciably affect the overall pooled estimate.</p>
<p>We have demonstrated in our 26 week FLEXX trail that there were no significant differences from saline in terms of adverse events and there were no joint effusions in the Euflexxa arm.³ [Altman et al., 2009] This is in line with the results from the AMELIA study indicating no significant difference in adverse events with repeat</p>	<p>The results from these 2 trials are presented in the report and have been synthesized with the results from other RCTs.</p>

Comment and Source	Response
<p>series of IA HA over 40 months.⁴ [Navarro-Sarabia et al., 2011]</p> <p>The commenter references a recent meta-analysis that included only trials (29 RCTs) using FDA-approved products:</p> <p>Miller LE, Block JE. US-Approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. <i>Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders</i> 2013;6 57-63.</p> <p>“When compared to the saline control there was a small to moderate treatment difference in the IA HA group from 4 to 26 weeks (SMD 0.43 at 4-13 weeks, 0.38 at 14-26 weeks; $p < 0.001$). There were no statistically significant differences in safety outcomes between IA HA and the Saline control (RD=0.7%(95%CI:-0.2%-1.5%,$p=0.12$)). “</p>	<p>This study appeared in a journal that is not indexed by MEDLINE or Embase, and was published in September 2013, after the update search (conducted in July 2013) for this report and thus was not included.</p> <p>The between-group effect size (0.43) reported by Miller and Block is somewhat larger than the corresponding effect size (0.37) reported in the Rutjes review. This might partially be explained by differences in how trial data were selected: outcomes at 4 to 13 weeks in the Miller and Block study and outcomes at the interval nearest 3 months in the Rutjes review. However, the study by Miller and Block offers no analysis of the relationship between outcomes and study size or study quality, whereas the Rutjes review showed that studies with larger sample sizes and clearly adequate assessor blinding were associated with a considerably smaller effect.</p> <p>The nonsignificant risk difference of 0.7% reported by Miller and Block refers to serious adverse events and is consistent with the risk difference <0.9% referred to in the report, based on the raw data serving as the basis of the Rutjes RR of 1.41 for serious adverse events. The report acknowledges reasons for uncertainty in interpretation of the Rutjes RR.</p> <p>The study by Miller and Block does not provide a comparison of trials using FDA-approved products with trials using non-FDA-approved products, which would be necessary to establish a statistically significant difference.</p>

Comment and Source	Response
September 4, 2013 Letter from HA Viscosupplementation Coalition; submitted via September 5 e-mail from Ken Long	
<p>Concerns about</p> <ol style="list-style-type: none"> 1. Evaluation of non FDA approved products 2. Non peer reviewed data included in analysis 3. Misleading definition of sham vs active controls 4. Lack of data to support comments on adverse events. 	<p>Please see responses in this document to other comments regarding concerns 1, 2, and 4.</p> <p><u>Additional comment on concern #2 regarding Rutjes lack of comment on whether published studies came from peer-reviewed journals:</u> Please see Appendix VIII in the report. Only 1 published study included in the Rutjes efficacy analysis was not included by other systematic reviews.</p> <p><u>Regarding concern #3:</u> The possibility that saline injection has a therapeutic effect is acknowledged in the report, but no evidence proving the effectiveness of saline injection or demonstrating how long the effect of saline could be expected to last was mentioned in the literature reviewed for the report, and no trials using no intervention controls were identified.</p>
<p>“We encourage Washington State HCA to consider that HA/Viscosupplements are currently covered by virtually every private health plan in the state. A decision to discontinue coverage for state employees and other beneficiaries of state funded services will single out these individuals and they will be disadvantaged.”</p>	<p>Thank you for providing this perspective.</p>
<p>“Finally, please note that HA/Viscosupplements are but one tool in the physician’s armamentarium. We recognize that some patients are better responders than others however this can be said with other therapies as well. From a safety standpoint, when compared to other common treatments, such as corticosteroids and NSAIDs, HA/Viscosupplements are far superior. With that said, please consider the consequences of a decision not to cover in terms of</p>	<p>Thank you for providing this perspective.</p>

Comment and Source	Response
critical adverse events, and increased rates of total knee replacements.”	
The commenters request that the systematic review, “US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials” (Miller and Block, 2013) be included in the report.	Please see responses in this document to other comments about this study. Inclusion would not change the conclusions of the report.
“The use of the effect size statistic to infer clinically meaningful changes in efficacy outcomes is frequently misinterpreted. For example, the control group-corrected treatment effect of viscosupplementation is frequently cited in meta-analyses (Rutjes et al. ¹ and others). However, it would be erroneous to estimate clinical relevance or responder rates from this statistic. In order to estimate the clinical benefit to a patient, the pre-treatment to post-treatment effect size in the viscosupplement group, not the placebo-corrected effect size, is the most appropriate statistic. Rutjes et al. ¹ report an effect size of 0.37 (corrected for control changes) and then erroneously state that this is equivalent to an improvement in knee pain or function of 0.9 points on a 0 to 10 scale. In fact, Rutjes’ reference for this statement ² was gleaned from other papers ³⁻⁶ that clearly state that pre-treatment to post-treatment treatment effects, not control group-corrected treatment effects, should be used to make this calculation.”	As justification for its MCID, the Rutjes review also cites a meta-analysis in which an effect size of 0.40, corresponding to a 1-cm difference on a 10-cm scale, was considered to represent a moderate effect in 2-arm trials of osteoarthritis treatments. The Rutjes review did not assume that group differences should be as large as within-group improvement from baseline, the latter of which has been defined in several sources as 20-mm improvement on a 100-mm scale.
“The meta-analysis of Miller and Block is the only paper to cite the pre-treatment to post-treatment SMD. Injection of US-approved viscosupplements resulted in an SMD for knee pain of 1.37 (95% CI: 1.12 to 1.61) at 4 to 13 weeks and 1.14 (95% CI: 0.89 to 1.39) at 14 to 26 weeks (both p<0.001). SMDs for knee function were 1.16	The relevance of the within-group (pretreatment/posttreatment) effects reported by Miller and Block would be clearer if Miller and Block had reported within-group effects for sham (saline) groups. Comparative improvement in the sham groups would be meaningful even if

Comment and Source	Response
<p>(95% CI: 0.99 to 1.34) and 1.07 (95% CI: 0.84 to 1.30), respectively (both p<0.001). These values represent very large treatment effects for viscosupplementation and are independent of the changes reported in saline control groups. Using the assumption that a standardized effect size of 0.37 equates to a 0.9 point improvement (on a 0 to 10 scale) in knee pain or function, the pre-treatment to post-treatment treatment effects for viscosupplementation reported by Miller and Block would be equal to improvements of 2.8 to 3.3 points for knee pain and 2.6 to 2.8 points for knee function (on a 0 to 10 scale). Importantly, the lower-bound confidence limits for all efficacy outcomes (ranging from 0.84 to 1.12) in the Miller & Block meta-analysis are substantially higher than the minimum threshold for clinical importance (0.37). <u>Therefore, it can reasonably be concluded that US-approved viscosupplements result in very large and clinically meaningful improvements in knee pain and function in most patients.</u> We recommend that the interpretation of these data are considered in the HTA Final Report. “</p>	<p>it is assumed there could be some therapeutic effect from saline injection.</p> <p>Furthermore, the report does include, in a prominent spot in the Overall Summary and Discussion section, reference to calculations of small effect size for some of the other common treatments for OA pain. This was intended to maintain the perspective that virtually any pain treatment has a placebo effect and that small between-group differences based on averages in placebo-controlled trials do not necessarily mean imperceptible improvement at the patient level.</p>
<p>“As stated in the OARSI guidelines, 7 there is 100% consensus that optimal management of osteoarthritis requires a combination of non-pharmacological and pharmacological modalities.”</p>	<p>This is an important consideration to keep in mind, and the report identifies the need for more studies that compare viscosupplementation as an add-on treatment with conventional treatment that includes other modalities but not viscosupplementation.</p>
<p>The commenters describe the effect sizes calculated by Miller and Block and calculated by the authors of the OARSI guidelines as being “among the highest reported for pharmacological therapies for knee osteoarthritis.”</p>	<p>It is problematic to try to rank treatments based on effect sizes that were calculated from different bodies of evidence.</p>
<p>“Overall, viscosupplementation has the most favorable risk-to-</p>	<p>Thank you for this perspective. As noted in the report, it is also</p>

Comment and Source	Response
benefit profile of any pharmacological modality for knee osteoarthritis treatment when considering magnitude of therapeutic effect, duration of therapeutic effect, consideration of therapy compliance, and safety risks.”	important to keep in mind that studies comparing viscosupplementation with NSAIDs have not differentiated between Cox inhibitors and nonselective NSAIDs, which differ in their safety profiles.
September 4, 2013 Letter from Brad Bisson, Samir Bhattacharyya, Julia Hwang, Brooks Story, and Suresh Aravind; DePuy Mitek, Inc.	
“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.”	Thank you for your comment.
“OA is a complex collection of pathologies for which no single therapy, including intra-articular (IA) HA, has demonstrated significant pain relief for all patients.”	In the <i>Other Considerations</i> section of the Evidence Summary, pooled estimates of effect for the full range of OA treatments are presented, to provide context for the evidence pertaining to HA injection.
“Clinical trials that focused on patients with unilateral, mild-to-moderate knee OA (as per the FDA approved indication) and using appropriate controls, have consistently shown clinically meaningful pain relief (Bannuru 2009, Bannuru 2011, Bellamy 2006, Hayes 2010, Reichenbach 2007, Samson 2007)”	Appendix IV, which presents the conclusions of the authors cited by the commenter, shows that these authors do not all agree that the evidence shows a clinically meaningful effect. See also the section on Systematic Review Authors’ Conclusions in the Evidence Summary.

Comment and Source	Response
<p>“IA HA is indicated for the treatment of mild-to-moderate OA of the knee. However, it has been our experience that physicians, in particular TKR specialists, often prescribe HA as a last-resort therapy to assure their patients with severe, end-stage OA that all nonsurgical options have been exhausted. In these patients, the likelihood of significant pain relief from any therapy is low, and we believe that such use of HA has contributed to the perception among some TKR surgeons that it is ineffective. Such use of IA HA in advanced OA patients, for whom it is not indicated, is reflected in a number of clinical trials that are included in one or more of the meta-analyses cited in the HTA draft evidence report. Several published trials (Jorgensen 2010, Lundsgaard 2008, Altman 2004, Karlsson 2002, Creamer 1994, Henderson 1994) included a significant fraction (23-42%) of either K-L Grade IV or Ahlbäck Grade II patients, indicative of an advanced disease state. All of these studies concluded that HA was not significantly better than placebo. Another unfavorable study (Dahlberg 1994) included only patients with knee injury but no evidence of OA. Yet another unfavorable study (Pham 2004) used a control group that received a daily oral placebo in addition to IA saline. Additionally, other studies reviewed used an HA injection regimen that is inconsistent with the FDA approved product labeling (example: use of 3 or 4 injections in a 26 week study with a product which is indicated for 26 weeks of pain relief, but only with a course of 5 injections). These negative conclusions are not indicative of the intended use of this class of products.”</p>	<p>The report acknowledges that there is some evidence that less severe OA is associated with greater benefit from HA injections, but pooled analyses showing the magnitude of benefit specific to populations with mild-to-moderate disease have not been published.</p> <p>In the study groups of the 21 trials reviewed for this report that had sample sizes ≥ 200 (and thus the greatest influence on pooled estimates), the most severe cases of OA were Kellgren-Lawrence grade III osteoarthritis, i.e., not bone on bone, in all but 4 studies and in those 4 studies, only some patients had Kellgren-Lawrence grade IV or Ahlbäck grade II disease.</p> <p>The small study (n=52) by Dahlberg et al. involved patients that were identified through records showing that “the arthroscopic examination established joint cartilage abnormalities” and reports of pain that “persisted for some time after discontinuation of exertion, as is seen in patients with radiographically demonstrated OA.” Only 34 of the 52 patients had a history of trauma.</p> <p>The HA group in the Pham study also received an oral placebo, thus maintaining an appropriate comparison between HA and saline injection.</p> <p>The commenters do not identify the studies that administered 3 to 4 injections of a product intended to be given with 5 injections or the sample sizes of those studies.</p>
<p>“Minimum Clinically Important Difference (MCID) was inappropriately applied in the most recent AAOS Clinical Practice Guideline (CPG). Moreover, questionable study selections biased</p>	<p>Distinction between within-group improvement and between-group differences, as well as the conclusions from the IMMPACT group, are presented in the report.</p>

Comment and Source	Response
<p>the results” “The draft HTA evidence report provides considerable discussion on the subject of minimum clinically important difference (MCID) and its application to the published clinical trials on the use of HA. There is not yet a universal agreement on what constitutes an acceptable MCID. Further, there is controversy over the application of MCID to the difference between HA and placebo, when the MCID was based on improvement from baseline from disparate therapies or derived from within patient improvements versus between group. We believe that such inappropriate use of MCID methodology was a major flaw of the recently published AAOS Clinical Practice Guidelines. The recommendations of the IMMPACT group state clearly that the decision to implement any OA therapy “. . . must be determined by a multi-factorial evaluation of the benefits and risks of the treatment and of other available treatments for the condition in light of the primary goals of therapy (Dworkin 2009). Differences in mean reductions in pain between active treatment and placebo groups do not adequately describe the potential benefits of a treatment in the population of individuals with chronic pain.” AAOS research also suffered from questionable study selections. For example, it included 3 HA products that are not approved for use in the US (Durolane, Adant, and Suplasyn). Moreover, it included one study (Heybeli) that compared arthroscopic debridement and HA usage.”</p>	<p>The report also acknowledges that the AAOS guidelines did not seem to be based on the full body of evidence. The evidence-based conclusions of the report were based on a systematic appraisal of the clinical research evidence, not practice guidelines.</p>
<p>“Rutjes meta-analysis does not address the causality or mechanisms of the serious side events, does not reflect the findings from other Level 1 meta-analyses, and has methodological challenges that could affect the conclusions” “In Key Question #2, there is general agreement with your</p>	<p>The statement about “high-quality” evidence and safety is followed by reference to pooled estimates in the Rutjes review showing no difference in <i>overall</i> adverse event rates between HA and control groups. In a separate paragraph, the Rutjes calculation suggesting an increased risk of serious</p>

Comment and Source	Response
<p>statement: “There is high-quality evidence that viscosupplementation is a safe procedure, at least in the short term.” Yet the Rutjes Systematic Review is then cited pertaining to the safety of viscosupplementation. The Serious Adverse Events (SAEs) listed in the Rutjes review, involve disparate body systems, unique patho-physiologies and appear unrelated to each other mechanistically. It is unclear how local IA injections of HAs can be attributed to such a diverse set of SAEs (such as cancer, GI, Cardiovascular) linked to different body systems. While an increase in reported adverse events are apparent, statistically, in the absence of a plausible biological mechanism that could generate these events, some form of biased ascertainment in reporting cannot be ruled out.</p> <p>Moreover, communication with the authors, indicate that of the 4 subjects with cancers (breast, prostate, squamous and melanoma) discovered within just 16-74 days post treatment, and were judged as “unrelated to HA treatment” by the investigators. “</p>	<p>adverse events is discussed, and concerns about this analysis similar to those expressed by the commenter are raised.</p>
<p>“Short term or long term use of NSAID may have increased risk of serious health problems and may not be advised in the OA population”</p> <p>“Of four guidelines used to update the draft HTA evidence report, one of the most recent, the AAOS, gave a “Strong” recommendation for the use of NSAIDs. With recent controversies surrounding the use of NSAIDs for patients with established CV disease (a large segment of the aging OA population), their usage would not only be restricted, but would require much more oversight (and costs) of patients to assure no harm. About 98</p>	<p>Thank you for your comments and this additional information regarding the alternatives to HA injection. Although this report was not intended to be a comparative effectiveness review, the report acknowledges in multiple places the reduced risk of GI events with HA injection, compared with NSAIDs or usual treatment that includes NSAIDs. The report also points out a particular gap in the evidence—the lack of comparative data regarding Cox inhibitors and HA injection.</p>

Comment and Source	Response
<p>million NSAID prescriptions were filled in 2012 and about 23 million people in the U.S. use over-the-counter NSAIDs on a daily basis. But these drugs are not benign; they can do harm to the kidneys, gastrointestinal tract, and cardiovascular system. In a recent publication in Circulation (Anne-Marie Schjerning Olsen, AM, et al., 2011), usage for NSAIDs in a nationwide cohort study concludes “Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view”. Liana Fraenkel, MD concluded in the paper “Treatment Options in Knee Osteoarthritis: The Patient’s Perspective”: When evaluating multiple alternatives, many older patients with knee osteoarthritis are willing to forgo treatment effectiveness for a lower risk of adverse effects. The patient treatment preferences derived in this study conflict with the current widespread use of nonselective NSAIDs in older patients with arthritis.”</p>	
<p>A recent meta analysis concludes that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee osteoarthritis.</p> <p>Miller and Block (2013) conducted a meta-analysis of randomized saline controlled clinical trials to determine the safety and efficacy of US-approved IA HA injections for symptomatic knee osteoarthritis.</p>	<p>See responses to other comments on the Miller and Block study.</p>
<p>“We acknowledge that HA viscosupplementation is not an effective</p>	<p>See earlier response to comments about OA severity.</p>

Comment and Source	Response
<p>therapy for all OA patients, but in those with mild to moderate knee OA, it provides significant pain relief and improved quality of life, with a well-established safety profile. We ask that you reconsider the negative conclusions of your report in light of these benefits and the unfortunate published reports on the misuse of HA therapy.”</p>	<p>Measurements of an impact on quality of life have produced conflicting results.</p>
<p>“Page 14: In Table 2, Summary of Findings regarding Adverse Events, a reminder again that “hylan” refers to one specific HA product. In addition, as noted earlier, relatedness to treatment is not addressed; gastrointestinal, cardiac, and cancer events have never been shown to be caused by or related to HA treatment.”</p>	<p>A qualifier, “causality uncertain” has been added to the Serious Adverse Events subheading in Table 2.</p>
<p>“Page 15: The two case series reports on long term results are for “hylan” only.”</p>	<p>The table has been edited accordingly.</p>
<p>“Page 16: Question #3, paragraph 1: We would agree with the findings that there is an opportunity for more studies to help specify the ideal candidates for HA treatment relative to the subpopulations of patients noted. However at this time, due to the overall safety and efficacy of US-approved products, there is very little patient risk, and HA treatments provide a significant non-surgical pain relief alternative and should continue to be offered as the clinical science is even more fully developed.”</p>	<p>Thank you for your comment and interpretation of the data.</p>
<p>“Page 19: Overall Summary and Discussion, paragraph 1, second sentence referencing the benefit may be too small. The IMMPACT guideline was previously referenced in the draft report. IMMPACT criteria is 10mm improvement from baseline. All pertinent studies show at least a 10mm baseline for US approved products.”</p>	<p>The IMMPACT criteria describe a 10-mm improvement as “small” and 20- to 27-mm improvement to be “moderate” or “clinically important.”</p>
<p>September 3, 2013 Letter from Yvonne Bokelman, Zimmer, Inc.</p>	

Comment and Source	Response
<p>2 missing publications: Effectiveness and Safety of a Multicenter Extension and Retreatment Trial of Gel-200 in Patients with Knee Osteoarthritis Cartilage October 2012 3: 297-304, first published on July 23, 2012 by V. Strand, et al. An article published in Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders entitled: US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials, and published on-line on September 2, 2013.</p>	<p>Thank you for calling this to our attention. The extension study by Strand et al. has been added to the report but does not alter the conclusions. The second article (by Miller and Block) was published after the last search conducted for this report. See remarks about this study in the response to other comments.</p>
<p>Missing information on Regence and GroupHealth guidance regarding prior authorization for HA injections</p>	<p>Thank you. The medication policies of Regence and GroupHealth have been added to the report.</p>
<p>“Hylan” refers only to Synvisc, not Gel-One.</p>	<p>Thank you. The report will be edited accordingly.</p>
<p>Regarding the comment in the report (Overall Summary and Discussion) that ““eventual recovery of function is uncertain”, HA injections are approved for pain relief, not restoration of function. “Page 5: Findings - In previous comments in an attempt to offer suggestions and clarifications with regard to the draft questions, with question 1A, we would again offer that viscosupplementation is not indicated as a treatment for osteoarthritis, but rather provides pain relief for osteoarthritis. We are concerned that the data may be misinterpreted as to HA’s efficacy (as referenced on Page 19, paragraph 1) with regard to the recovery of function, when HA injections are indicated for pain relief.”</p>	<p>The report correctly states the FDA approval for the indication of pain relief. Restoration of function is a related, patient-important outcome.</p>
<p>“In paragraph three of this section [Policy Context], the conclusion that there are serious safety concerns based on the Rutjes article is inappropriate due to the poor quality of the data and the flawed</p>	<p>No conclusions are stated in the Policy Context. The problems associated with interpreting the Rutjes estimate of increased risk of serious adverse events are discussed in the report,</p>

Comment and Source	Response
methodologies.”	which concludes that viscosupplementation is a safe treatment in the short term and that there is insufficient evidence to draw conclusions about long-term safety.
“ . . . it is noted that the “American College of Radiology” has issued guidelines in the last sentence of the paragraph. This should be corrected to reflect the American College of Rheumatology.”	Thank you for pointing out this typing error! It has been corrected.
“Page 6: Paragraphs 4 and 5 referencing trial results regarding responder rates and loss of follow-up: At least for the study of Gel-One, we found that the responder rate in our study was considerably higher than that which is reported in paragraph 4 using OMERACT-OARSI responder criteria. In paragraph 5, the high loss of follow-up provides a generalized negative connotation which again was not the experience in the Gel-One study.”	Paragraph 5 has been revised to reflect the Gel-One extension study of Strand et al. However, this extension trial was likewise subject to high loss to follow-up between the end of the original trial and the extension phase, i.e., almost 40% of patients enrolled in the original trial declined to participate in the extension trial. Paragraph 4 has been corrected to show an NNT range of 7 to 16 (rather than 7 to 13) in the trials with positive results.
“Page 11: In paragraph 2, there is a suggestion of no difference between FDA and non-FDA approved products. We disagree with that statement, and believe that there is a difference when studying US versus OUS products. This is evidenced in the results of the meta-analysis published in Clinical Medicine Insights noted above.”	See previous comments on lack of direct comparisons between FDA-approved and other products and implications of the meta-analysis (Miller and Block) in Clinical Medicine Insights.
“Page 15: The two case series reports on long term results are for “hylan” only.”	A note has been added.
“Page 16: Question #3, paragraph 1: We would agree with the findings that there is an opportunity for more studies to help specify the ideal candidates for HA treatment relative to the subpopulations of patients noted. However at this time, due to the overall safety and efficacy of US-approved products, there is very little patient risk, and HA treatments provide a significant non-surgical pain relief alternative and should	Thank you for your interpretation of the findings.

Comment and Source	Response
<p>continue to be offered as the clinical science is even more fully developed.”</p>	
<p>“Page 20: Other Considerations, last paragraph on the page, suggesting MCID for “understanding group differences” in trials is inappropriate, per Dr. Dworkin. This is where the area of conflict developed with the AAOS Clinical Practice Guidelines, and the inappropriate application of MCID. Dr. Dworkin appeared before members of the CPG Committee to try to explain and redirect them on the appropriate use of MCID, which specifically is not using MCID/MCII to compare groups.”</p>	<p>The reference in this paragraph to Dr. Dworkin’s statements only has to do with the magnitude of benefit from other pain treatments. Dr. Dworkin’s comments on the importance of distinguishing between within-group and between-group differences and putting more emphasis on responder rates than average differences are reflected in other parts of the report.</p>
<p>“Page 34: Under Pain, and in the fourth bullet point, the third sentence about IMMPACT contradicts the draft evidence report’s earlier discussion about MCID.”</p>	<p>Several edits have been made to clarify the implications of the IMMPACT distinction between within-group and between-group improvements.</p>
<p>The commenter objects to Hayes’ application of the concept of minimal clinically important difference (MCID), which is defined in terms of an individual’s improvement relative to baseline, not in terms of differences between a treatment group and a control group. The commenter refers to confusion over this issue in development of the AAOS guidelines and the FDA’s decision to drop the concept from its industry guidance because of the confusion attached to it.</p>	<p>Hayes understands how definitions of clinically meaningful improvement are derived and the problems associated with applying them to between-group differences. In the Evidence Summary, trials reporting responder rates, which is the preferred analytic approach in the IMMPACT statement, are emphasized for assessing clinical relevance. An additional comment has been added to the discussion of MCID in the Technical Report to clarify that clinically meaningful between-group differences may be smaller than clinically meaningful within-group improvement relative to baseline.</p> <p>It should also be noted that the MCID assumed by the Rutjes review (SMD, 0.37) corresponds to a 0.9-mm difference, not the 20-mm improvement defined by several experts as signifying clinically important improvement from baseline;</p>

Comment and Source	Response
	<p>the Rutjes assumption thus seems reasonable for a between-group effect.</p> <p>The evidence-based conclusion of the report reads “the magnitude of benefit of HA may be too small to be clinically important for many if not most patients,” which is consistent with the following: (1) a reasonable assumption that if the average effect just meets or slightly exceeds the threshold for clinical importance (even taking the IMMPACT view into account), many and possibly most patients do not experience meaningful benefit; (2) less than clinically meaningful effect when analysis is restricted to better-quality studies (Rutjes stratified analysis); and (3) variable findings from studies that reported response rates based on within-group (relative to baseline) definitions of clinically meaningful response.</p>

September 4, 2013

Mr. Josh Morse, MPH
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Thank you for the opportunity to provide a response to the draft evidence report on Viscosupplementation for Knee Osteoarthritis.

Bioventus LLC. is a biologics company that delivers clinically proven, cost-effective products that help people heal quickly and safely. The company's innovative products include market-leading devices, therapies and diagnostics that make it a global leader in active orthopaedic healing. Built on a commitment to high quality standards, evidence-based medicine, and strong ethical behavior, Bioventus is a trusted partner for physicians worldwide.

Bioventus markets SUPARTZ® Joint Fluid Therapy, an injectable solution of highly purified sodium hyaluronate (hyaluronan) 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.

We support your pursuit of evidence based evaluations of efficacy and cost effectiveness and are committed to advancing the research on OA treatments, specifically hyaluronic acid based products. We are backing up our commitment with significant funding for clinical and economic studies for OA treatment, and for advanced formulations of HA products to reduce administration cost and to improve effectiveness.

Enclosed please find our response to the key questions you have posed, and the draft evidence report from Hayes.

We look forward to the opportunity to present key portions of the content to the committee in the weeks ahead. In the interim, please advise if you have any questions about the attached information. Thank you for your consideration.

Sincerely,

Peter Heeckt, MD, PhD
Chief Medical Officer

Response Evidence Report and Background on Viscosupplementation for Knee Osteoarthritis

Bioventus appreciates the opportunity to reply to the HTA draft evidence report on Hyaluronic Acid/Viscosupplementation for knee osteoarthritis. We support evidence based policy development and are committed to working with the clinical community and payers in this process. We have organized our comments around several important points that we ask the committee to consider.

BACKGROUND

Viscosupplementation, also referred to as intra-articular hyaluronic acid injection (IA-HA), provides an important FDA-approved treatment for patients with OA of the knee. IA-HA provides the only available intra-articular (ia) analgesic for OA treatment, and the only device that is essentially free of systemic adverse events and drug interactions. It is a cost effective OA treatment, vital as an alternative to surgical interventions, is a critically important option for patients with GI or CV comorbidities for whom chronic NSAID administration is contraindicated, and for patients who are not good candidates for total knee replacement (TKR). In clinical practice, the goal of treatment with viscosupplementation is, often in parallel with other treatments, to treat pain and to increase function.

FDA APPROVAL

The FDA PMA approval of the six IAHA products on the market in the US is based on a careful FDA review of randomized clinical trial data demonstrating safety and effectiveness. It is widely recognized that HA products vary in concentration, dose size, dose frequency, molecular weight, purity and formulation. It's important to note that there are multiple HA products, approved elsewhere in the world that have not met the stringent FDA threshold and therefore are not approved or available in the US.

With this in mind, when evaluating the IAHA "class", it is inappropriate to include products that have not passed the stringent FDA approval process. Please note that two recent meta-analyses, Rutjes et al.¹ and the 2013 AAOS² evaluation both included multiple studies of products that are not available in the US market. These reviews incorrectly implicitly assumed that all IAHA products, regardless of approval status in the US, are equally as effective.

DEFINITION OF PLACEBO

According to the medical dictionary, the definition of a placebo is:

An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.

Saline injection, used as a control in many IAHA studies, does not meet the definition of a placebo, as the word is intended. Saline involves insertion of a needle into a joint space, aspiration of effusion (along with inflammatory cytokines), and injection of a diluent, further diluting the pain mediators in the synovium. This is an active treatment and is improperly referenced as a “placebo” or “sham”.

Conclusions based on calculations of effectiveness of IAHA on performance vs. saline injections, without consideration of baseline improvement, are not valid indicators of efficacy. This is especially true when calculating minimal clinical important improvement (MCII). In practice, MCII should be a measure of the patient reported improvement from baseline. Both Rutjes and AAOS inappropriately measured MCII as a group mean delta between saline and IAHA.

Only one recent systemic review focused on US based IAHA products and correctly measured effectiveness based on the delta between pre and post treatment. The analysis concluded that “...this systematic review and meta-analysis of randomized, saline controlled trials confirms that intra-articular injections of US approved HA products is safe and efficacious in patients with symptomatic knee OA”.³

META-ANALYSES DATA SOURCES

Good quality meta-analyses are partially based on the quality of data inputs. Generally, peer reviewed clinical data is considered good quality and appropriate for inclusion when pooling data for meta-analyses. Unfortunately Rutjes et al. included data from non-peer reviewed sources including “content experts”, “conference proceedings”, “review articles” and “clinical trial registries”. There is no way to verify the validity of the data inputs and as such the results, and conclusions must be considered equally invalid.

ALTERNATIVE TREATMENTS

Corticosteroids

IA HA Effectiveness vs. Corticosteroids:

Although corticosteroids are FDA approved for synovitis rather than OA knee pain, the effectiveness of IA-HA as compared to corticosteroids has been evaluated in several peer reviewed publications. In a study published in Arthritis and Rheumatism, December 2009⁵, the author conducted a meta-analysis of

9 different clinical studies comparing IA corticosteroids with IA hyaluronic acid injections. Their conclusion was that from baseline to week 4, IA corticosteroids appear to be more effective for pain, from week 4-8, the two treatments had equal efficacy, but beyond week 8 (up to 26 weeks), IA-HA acid had greater efficacy than IACS. As such it can be concluded that though corticosteroids may be effective for short term relief, they are no better overall than IA-HA when considered over a 6-month period. Additionally, IACS injections are limited in the total number that may be given any one patient.

The comparison with corticosteroids was also noted in the 2008 OARSI Guidelines. Recommendation #17 reads, "Injections of IA hyaluronate may be useful in patients with knee or hip OA. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids".

It is important to note that IACS administration involves important safety considerations, and contraindications clearly noted in CS labeling, which makes their routine repeat use in knee OA both impractical and potentially dangerous.

IAHA Safety vs. Corticosteroids:

There is a profound safety difference between IA-HA and IACS, related to their fundamentally different mechanism of action. Corticosteroids are potent anti-inflammatory drugs, and as such can depress immune function and shift tissue metabolism. Corticosteroid injections must be used cautiously because of their multiple drug interactions (aspirin, anticoagulants, diuretics, estrogen, phenytoin, rifampin, phenobarbital, macrolide antibiotics/antifungals such as erythromycin, ketoconazole, and diabetes drugs) and their contraindication in patients with many types of comorbidities (hypersensitivity, pituitary or adrenal hypofunction, osteoporosis, infection, compromised immune system, etc.) Contraindications to intra-articular glucocorticoid injection include infection in or around the joint, bacteremia or sepsis, significant skin breakdown at the injection site, osteochondral or other intra-articular fracture at the joint to be injected, and severe joint destruction¹⁰. Other, uncommon potential side effects of intra-articular glucocorticoid treatment include tendon weakening and rupture, fat and skin atrophy, and muscle wasting precipitated by misdirected injections; nerve and blood vessel damage, due to misdirected injections; steroid arthropathy; and systemic effects caused by high doses and simultaneous injection of multiple joints. Post-injection flares can also occur in about 2% to 6% of patients and are believed to result from chemical synovitis in response to the injected crystals.

According to one author, and often recommended in practice, after a corticosteroid injection in the knee, the patient should remain in bed or at rest and avoid walking as much as possible for 3 days, and then use crutches or cane for the next 2 to 3 weeks.

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

Safety vs. Non Steroidal Anti-Inflammatory Drugs (NSAIDs):

Although commonly prescribed for OA knee pain, NSAIDs pose a substantial and well documented safety risk, and in fact are contraindicated for many patients due to the high number of gastrointestinal (GI) and cardiovascular (CV) comorbidities. NSAIDs are also associated with a high mortality rate and a high number of hospitalizations each year¹². Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for non-steroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone according to the American Journal of Medicine.

The number of CV adverse events associated with NSAID use is similarly troubling. These side effects of chronic NSAID administration are especially common in OA patients due to the chronic, slowly degenerating character of the disease, and the association with long term utilization. The tremendous burden placed on health care systems for treating the CV and GI complications of NSAIDs are significant drawbacks to their recommended use in knee OA patients, especially as long term therapy for the chronic pain of osteoarthritis.

In 2005, in the wake of the Vioxx and Bextra recall, the FDA required NSAID manufacturers to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular events and the well described, serious, potential life-threatening gastrointestinal bleeding associated with their use. No such warnings are needed for IA-HA products.

Please note the following quote from the 2013 AAOS Guideline on Treatment of OA of the Knee, “We base evidence grades on the quality and applicability ratings, whether or not the studies report critical outcomes, and potential harm to patients.” As such, it is highly important to note that in the development of the AAOS Guidelines in 2013, there was no evaluation or consideration of safety. As such, an effective, yet dangerous treatment such as NSAIDs received a positive recommendation from the society.

In conclusion, Viscosupplements offer essential, safe and effective disease management in many patients as an alternative to both NSAIDs and corticosteroids.

SUMMARY

We understand that Washington State HCA has chosen to re-review HA-Viscosupplements based on the publication of Rutjes et al. in 2012. As we noted above, this review has many flaws and cannot be considered valid new evidence upon which to base a decision to continue coverage.

Lastly we wish to bring to your attention the fact that Viscosupplements are a covered benefit by Medicare AND by every private insurance carrier in the state of Washington. A decision to cease coverage for those receiving state benefits will serve to single out and dis-advantage this patient population.

1. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157(3):180-191.
2. <http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf>
3. Miller L, Block J. US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials <http://www.la-press.com/us-approved-intra-articular-hyaluronic-acid-injections-are-safe-and-ef-article-a3856-abstract>

From: Dasa, Vinod <vdasa@lsuhsc.edu >
To: HCA ST Health Tech Assessment Prog
Sent: Wed 9/4/2013 1:58 PM
Cc:
Subject: Public Comment for: Hyaaluronic Acit/Viscosupplementation

To Whom it May Concern,

After reviewing the draft by Hayes inc on HA injections, I would like to point to some important clinical considerations:

- 1) Rutjes et al. and AAOS included non FDA HA products in their analysis. There is likely a reason many products around the world have not been approved by the FDA, because they did not demonstrate adequate safety of efficacy
- 2) The AAOS guidelines only gave positive recommendations to 3 treatments (weight loss, NSAID's, and exercise). They were also unable to demonstrate pain relief with narcotic or steroid injections for arthritic knee pain (both inconclusive) which are both the mainstays of treatment for millions of patients. This makes very little clinical sense given the experience of millions of patients and physicians.
- 3) Many of the publications used in the various meta analyses were methodologically flawed. One example is inclusion of patients w bone on bone OA. It has been well studied that patient w severe OA will not benefit from HA injections. Thus it's no wonder effect size compared to saline in some trials was minimal. How can one expect a patient w bone on bone OA to receive any relief with HA when the only treatment that will work is a knee replacement?
- 4) Rutjes et al included non peer reviewed or non published information such as brochures, emails, conference proceedings... how can one possibly analyze information from this low quality evidence?
- 5) 2 authors reviewed in the rutjes et al review , Mcalindon et al and Navarro et al, have submitted letters to the editor questioning rutjes et al's interpretation of their data
- 6) The serious AE inference in the Rutjes et al is without any clinical merit. From a regulatory perspective the FDA has not recalled or found any reason to question the safety of any US approved HA injections. From a biologic perspective, there is no plausible explanation based on current medical knowledge for HA injections to cause an AE such as cancer. This statement by Rutjes et al is sensationalistic w no biologic foundation. OF the millions of injections given worldwide, why is this the first ever recognition of these serious AE's? Have these AE's managed to escape the view of all the regulatory agencies worldwide (including FDA), corporations, physicians, registries, specialty societies, and patients for over 20 years? This alone may call into question the motives and validity of Rutjes et al.
- 7) There have been many statistical debates and questions around the continuous reanalysis of various analyses which has become mind numbing to the point where the average physician can no understand what is reality.
- 8) The current paradigm of NSAID's and steroid injections create additional cost from their medical complications especially when compared to HA injections which are not accounted for in reviews such as this.
- 9) HA injections from a basic science perspective have been found to be chondroprotective which is very important if we are trying to lower the arthroplasty burden.
- 10) Patients w mild to moderate OA do benefit from HA injections whereas patients with bone on bone OA will not benefit.

11) Nsaid's and narcotics are not the answer to OA treatment and will only increase harm and cost. Decisions that eliminate safe alternatives such as HA injections will invariably lead to increased surgery and in turn undermine an important objective of the current healthcare climate which is to create value and control cost.

Sincerely,

Vinod Dasa MD
Associate Professor
Department of Orthopaedic Surgery
Louisiana State University Health Sciences Center
New Orleans, Louisiana
www.medschool.lsuhscc.edu/orthopaedics/research.aspx

September 4, 2013

Washington State Health Technology Assessment (HTA) Program

RE: Coverage Guidance: Viscosupplementation for Osteoarthritis of the Knee

Dear Washington State HTA members,

Thank you for the opportunity to allow us to provide comments on the continuation of coverage for *Viscosupplementation for Osteoarthritis of the Knee*. 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.

OA is a complex collection of pathologies for which no single therapy, including intra-articular (IA) HA, has demonstrated significant pain relief for all patients. It is thus important that clinicians have access to a wide range of therapies for the treatment of knee OA due to the variation in patients' needs, co-morbidities, and response to therapy. Nonsurgical treatment options have limitations in treating this chronic disease. NSAIDs may cause cardiovascular and gastrointestinal complications with repeated use. IA injections of corticosteroids often provide short term pain relief, but are known to potentially cause long-term cartilage and tendon damage. For this reason, surgeons often prescribe no more than one injection every 3 months which can lead to painful periods between courses of treatment. Weight loss, exercise and physical therapy can be beneficial to some patients, but are often ineffective due to high rates of patient non-compliance. For patients who have not obtained sufficient pain relief from such therapies, total knee replacement (TKR) surgery may be considered.

Clinical trials that focused on patients with unilateral, mild-to-moderate knee OA (as per the FDA approved indication) and using appropriate controls, have consistently shown clinically meaningful pain relief (Bannuru 2009, Bannuru 2011, Bellamy 2006, Hayes 2010, Reichenbach 2007, Samson 2007)

HA is an IA therapy for OA of the knee in patients who have not had an adequate response to conservative treatment or simple analgesics, who are seeking a longer duration of pain relief compared to IA steroid injections, and/or who may wish to delay surgery. IA HA is indicated for the treatment of *mild-to-moderate* OA of the knee. However, it has been our experience that physicians, in particular TKR specialists, often prescribe HA as a last-resort therapy to assure their patients with severe, end-stage OA that all nonsurgical options have been exhausted. In these patients, the likelihood of significant pain relief from any therapy is low, and we believe that such use of HA has contributed to the perception among some TKR surgeons that it is ineffective. Such use of IA HA in advanced OA patients, for whom it is not indicated, is reflected in a number of clinical trials that are included in one or more of the meta-analyses cited in the HTA draft evidence report. Several published trials (Jorgensen 2010, Lundsgaard 2008, Altman 2004, Karlsson 2002, Creamer 1994, Henderson 1994) included a significant fraction (23-42%) of either K-L Grade IV or Ahlbäck Grade II patients, indicative of an advanced disease state. All of these studies concluded that HA was not significantly better than placebo. Another unfavorable study (Dahlberg 1994) included only patients

with knee injury but *no evidence of OA*. Yet another unfavorable study (Pham 2004) used a control group that received a daily oral placebo in addition to IA saline. Additionally, other studies reviewed used an HA injection regimen that is inconsistent with the FDA approved product labeling (example: use of 3 or 4 injections in a 26 week study with a product which is indicated for 26 weeks of pain relief, but only with a course of 5 injections). These negative conclusions are not indicative of the intended use of this class of products.

Minimum Clinically Important Difference (MCID) was inappropriately applied in the most recent AAOS Clinical Practice Guideline (CPG). Moreover, questionable study selections biased the results

The draft HTA evidence report provides considerable discussion on the subject of minimum clinically important difference (MCID) and its application to the published clinical trials on the use of HA. There is not yet a universal agreement on what constitutes an acceptable MCID. Further, there is controversy over the application of MCID to the difference between HA and placebo, when the MCID was based on improvement from baseline from disparate therapies or derived from within patient improvements versus between group. We believe that such inappropriate use of MCID methodology was a major flaw of the recently published AAOS Clinical Practice Guidelines. The recommendations of the IMMPACT group state clearly that the decision to implement any OA therapy “. . . must be determined by a multi-factorial evaluation of the benefits and risks of the treatment and of other available treatments for the condition in light of the primary goals of therapy (Dworkin 2009). Differences in mean reductions in pain between active treatment and placebo groups do not adequately describe the potential benefits of a treatment in the population of individuals with chronic pain.” AAOS research also suffered from questionable study selections. For example, it included 3 HA products that are not approved for use in the US (Durolane, Adant, and Suplasyn). Moreover, it included one study (Heybeli) that compared arthroscopic debridement and HA usage.

Rutjes meta-analysis does not address the causality or mechanisms of the serious side events, does not reflect the findings from other Level 1 meta-analyses, and has methodological challenges that could affect the conclusions

In Key Question #2, there is general agreement with your statement: “There is *high-quality* evidence that viscosupplementation is a safe procedure, at least in the *short term*.” Yet the Rutjes Systematic Review is then cited pertaining to the safety of viscosupplementation. The Serious Adverse Events (SAEs) listed in the Rutjes review, involve disparate body systems, unique patho-physiologies and appear unrelated to each other mechanistically. It is unclear how local IA injections of HAs can be attributed to such a diverse set of SAEs (such as cancer, GI, Cardiovascular) linked to different body systems. While an increase in reported adverse events are apparent, statistically, 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 the authors, indicate that of the 4 subjects with cancers (breast, prostate, squamous and melanoma) discovered within just 16-74 days post treatment, and were judged as “unrelated to HA treatment” by the investigators.

Short term or long term use of NSAID may have increased risk of serious health problems and may not be advised in the OA population

Of four guidelines used to update the draft HTA evidence report, one of the most recent, the AAOS, gave a “Strong” recommendation for the use of NSAIDs. With recent controversies surrounding the

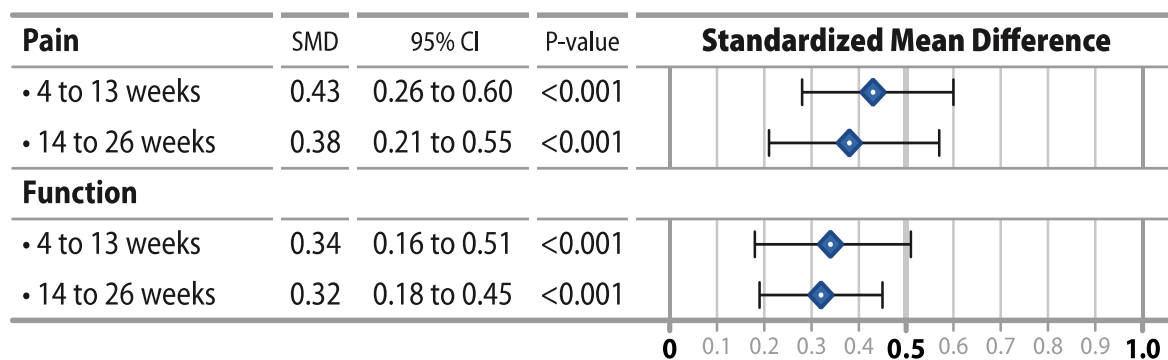
use of NSAIDs for patients with established CV disease (a large segment of the aging OA population), their usage would not only be restricted, but would require much more oversight (and costs) of patients to assure no harm. About 98 million NSAID prescriptions were filled in 2012 and about 23 million people in the U.S. use over-the-counter NSAIDs on a daily basis. But these drugs are not benign; they can do harm to the kidneys, gastrointestinal tract, and cardiovascular system. In a recent publication in *Circulation* (Anne-Marie Schjerning Olsen, AM, et al., 2011), usage for NSAIDs in a nationwide cohort study concludes “Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view”. Liana Fraenkel, MD concluded in the paper “Treatment Options in Knee Osteoarthritis: The Patient’s Perspective”: When evaluating multiple alternatives, many older patients with knee osteoarthritis are willing to forgo treatment effectiveness for a lower risk of adverse effects. The patient treatment preferences derived in this study conflict with the current widespread use of nonselective NSAIDs in older patients with arthritis.

A recent meta analysis concludes that intra-articular injection of US-approved HA products is safe and efficacious in patients with symptomatic knee osteoarthritis

Miller and Block (2013) conducted a meta-analysis of randomized saline controlled clinical trials to determine the safety and efficacy of US-approved IA HA injections for symptomatic knee osteoarthritis.

The study included 29 studies representing 4,866 unique subjects and found that IA HA injections “... resulted in very large treatment effects between 4 and 26 weeks for knee pain and function compared to pre-injection values, with standardized mean difference (SMD) values ranging from 1.07 to 1.37 (all $p < 0.001$). Compared to saline controls, SMDs with IA HA ranged from 0.38-0.43 for knee pain and 0.32-0.34 for knee function (all $p < 0.001$). There were no statistically significant differences between IAHA and saline controls for any safety outcome, including serious adverse events (SAEs) ($p = 0.12$), treatment-related SAEs ($p = 1.0$), study withdrawal ($p = 1.0$), and AE-related study withdrawal ($p = 0.46$).” It is to be noted that most, but not all, studies included in this research, quite appropriately, excluded subjects with end-stage (Kellgren-Lawrence grade IV or equivalent) knee OA.

The following figure shows the SMD for IA HA injection versus saline controls (Miller and Block).



We acknowledge that HA viscosupplementation is not an effective therapy for **all** OA patients, but in those with mild to moderate knee OA, it provides significant pain relief and improved quality of life, with a well-established safety profile. We ask that you reconsider the negative conclusions of your report in light of these benefits and the unfortunate published reports on the misuse of HA therapy.

We concur with your 2010 HTA conclusions that the “. . . evidence on Hyaluronic Acid / Viscosupplementation demonstrates that there is sufficient evidence to cover with conditions the use of Hyaluronic Acid / Viscosupplementation for the treatment of pain associated with OA.” In conclusion, we strongly believe that the clinical evidence cited above supports the continued listing of viscosupplementation with HAs as a covered benefit for the treatment of pain associated with OA of the knee.

If you have any questions about the information included in this letter or require additional information, please contact us.

Sincerely,

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Dear Mr. Morse,

We appreciate the opportunity to provide further comment on the Hyaluronic Acid (HA)/Viscosupplementation draft evidence report.

Ferring's research activities and products are connected by a common thread focused on the provision of tailored treatments that work on the body's own terms to enable doctors to combat diseases and medical conditions including osteoarthritis. Ferring is committed to working with the scientific community, consumer groups and payers to provide transparent and accurate information on HA/Viscosupplements to help physicians and their patients make better health care decisions.

We maintain our position that viscosupplementation with HA is an effective and safe option for patients unable to achieve adequate pain relief with other interventions or who cannot tolerate adverse events associated with acetaminophen, non-steroidal anti-inflammatory drugs, or corticosteroid injections, or those who are unwilling to accept the well-known risks associated with these drugs. I hope that this safe and effective option will not be denied to the state employees.

It is our understanding that Washington State is re-reviewing the HA/Viscosupplements and in doing so is relying on a recent publication, *Viscosupplementation for Osteoarthritis of the Knee*, authored by Rutjes et al. in the August 2012 *Annals of Internal Medicine*.

Although methodology used in the meta-analysis of intraarticular (IA) HA is exemplary in many regards, there are still some significant concerns in the study methodology that need to be considered when evaluating the study conclusions. These concerns range from the utilization of data from non FDA approved products, the use of unpublished data, and potentially misleading information regarding the safety of the class of products.¹

A primary concern of the analysis by Rutjes et al, is that it consist of US and non-US products. Of the 15 products included in the analysis, only six of were FDA approved. We cannot be certain if non FDA approved products would meet the current safety, efficacy and manufacturing standards required for here in the US. Due to the inclusion of ex-US products, the applicability of this analysis to the US population comes into question. It is clear that there are many differences in the sourcing of products (avian or bacterial), molecular weight, structural and purification processes.² Furthermore, nearly a third of the data incorporated were not from peer reviewed full print journals including content experts, poster presentations, review articles, and clinical trial registries. The inability to disclose the contributory data calls into question the transparency of the analysis. We also contend that the potential harm of viscosupplementation with hyaluronic acid for treatment of OA kneed pain does not exceed the

potential benefits as stated in the current draft of the clinical practice guidelines. We have demonstrated in our 26 week FLEXX trial that there were no significant differences from saline in terms of adverse events and there were no joint effusions in the Euflexxa arm.³ This is in line with the results from the AMELIA study indicating no significant difference in adverse events with repeat series of IA HA over 40 months.⁴

A recently published systematic review and meta-analysis was conducted in order to address some of the concerns that were brought to light from the Rutjes et al. analysis.⁶ This peer-reviewed paper titled *“US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials”*, is the most recent meta-analysis available on the topic and is more applicable to the US market. The methodology called for the exclusion of any studies that utilized non-FDA approved viscosupplementation, only including primary published peer-reviewed literature that compared HA with a saline control. These differences address some of the common limitations of other systematic reviews of the class.

The analysis including 29 studies representing 4,866 subjects (IA HA; 2,673, Saline 2,193) resulted in very large treatment effect and function when compared to pre-injection values (standardized mean difference(SMD) 1.37 at 4-13 weeks, 1.14 at 14-16 weeks; $p < 0.001$). When compared to the saline control there was a small to moderate treatment difference in the IA HA group from 4 to 26 weeks (SMD 0.43 at 4-13 weeks, 0.38 at 14-26 weeks; $p < 0.001$). There were no statistically significant differences in safety outcomes between IA HA and the Saline control (RD=0.7%(95%CI:-0.2%-1.5%, $p=0.12$)).

Based on the results of this new analysis consisting of only US-approved products, it is evident that not all HA products are the same and those available outside the US may not be held to the same standards required by the FDA. Limiting the analysis to strictly US approved products allows for more consistent and applicable results to the relevant US population. It seems evident that US-approved viscosupplementation is not only safe but also efficacious in patients with symptomatic knee osteoarthritis and we request that this new analysis be considered in the final HTA Report.

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HA VISCOSUPPLEMENT COALITION

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Dear Mr. Morse,

On behalf of the Hyaluronic Acid Viscosupplement Coalition (HAVC), thank you for the opportunity to comment on the Hyaluronic Acid/Viscosupplementation draft evidence report.

The HAVC is a collaborative of hyaluronic acid injection manufacturers (Bioventus LLC, Durham, NC; DePuy Synthes Mitek Sports Medicine, Raynham, MA; Ferring Pharmaceuticals Inc., Parsippany, NJ; Fidia Pharma USA, Inc., Parsippany, NJ; Zimmer, Inc., Warsaw, IN) and Advamed, the Advanced Medical Technology Association. The group is committed to working with the scientific community, consumer groups and payers to provide transparent and accurate information on HA/Viscosupplements to help physicians and their patients make better health care decisions.

We understand that Washington State is re-reviewing the HA/Viscosupplements based on the publication of a recent review article, *Viscosupplementation for Osteoarthritis of the Knee*, authored by Rutjes et al. in the August 2012 Annals of Internal Medicine. Because there are significant concerns regarding the methodology and conclusions of the authors, our belief has been that the review does not represent credible new evidence regarding the safety and efficacy of Hyaluronic/Viscosupplement products.

Our concerns about the Rutjes review article can be broken down into four focus areas:

1. Evaluation of non FDA approved products
2. Non peer reviewed data included in analysis
3. Misleading definition of sham vs active controls
4. Lack of data to support comments on adverse events.

FDA Approved Injections

Only 6 hyaluronic acid/viscosupplementation products have been approved by the FDA for use in the United States, (Supartz, Hyalgan, Orthovisc, Synvisc, Gel One, and Euflexxa). Rutjes et al included 9 additional unapproved 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. In fact a repeat analysis using only FDA approved products was conducted and recently published which yielded markedly different outcomes in efficacy and safety compared to Rutjes et al. The study (Miller & Block-Please see link in the first section of our detailed comments) confirms that not all HA/Viscosupplements are the same, and those available outside the US are not held to the standards that the FDA requires for approval in the US market. As such we object to the use of data from products not approved in the US to generalize about the HA/Viscosupplement class.

Non Peer Reviewed Data

Rutjes et al. utilized non-peer reviewed data including “content experts”, “conference proceedings”, “review articles” and “clinical trial registries”. Data from non-peer reviewed sources 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.

Misleading Definition of Sham

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 should be considered an active control. Aspiration of synovial fluid followed by injection of saline is indeed a reimbursed 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.

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.

Reimbursement Status

We encourage Washington State HCA to consider that HA/Viscosupplements are currently covered by virtually every private health plan in the state. A decision to discontinue coverage for state employees and other beneficiaries of state funded services will single out these individuals and they will be disadvantaged.

Finally, please note that HA/Viscosupplements are but one tool in the physician's armamentarium. We recognize that some patients are better responders than others however this can be said with other therapies as well. From a safety standpoint, when compared to other common treatments, such as corticosteroids and NSAIDs, HA/Viscosupplements are far superior. With that said, please consider the consequences of a decision not to cover in terms of critical adverse events, and increased rates of total knee replacements.

In the following pages, please find our specific comments on the Hayes draft, Hyaluronic Acid/Viscosupplementation –Draft Evidence report.

Again, thank you for the opportunity to comment.

Best regards,

HAVC

Hyaluronic Acid/Viscosupplementation Coalition

Bioventus LLC, Durham, NC; DePuy Synthes Mitek Sports Medicine, Raynham, MA; Ferring Pharmaceuticals Inc., Parsippany, NJ; Fidia Pharma USA, Inc., Parsippany, NJ; Zimmer, Inc., Warsaw, IN

Comments from HA Viscosupplement Coalition (HAVC)

Bioventus LLC, Durham, NC; DePuy Synthes Mitek Sports Medicine, Raynham, MA; Ferring Pharmaceuticals Inc., Parsippany, NJ; Fidia Pharma USA, Inc., Parsippany, NJ; Zimmer, Inc., Warsaw, IN

Search Strategy and Selection Criteria (p. 3)

We would like to bring a recently published systematic review and meta-analysis to the attention of Hayes, Inc. This peer-reviewed paper titled *“US-Approved Intra-Articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized, Saline-Controlled Trials”*, is the most relevant meta-analysis available on the topic for the following reasons:

- a) It is the most recent meta-analysis available, published in September 2013,
- b) Only studies of US-approved viscosupplements were included
- c) Only studies with saline-controls were included.

<http://www.la-press.com/us-approved-intra-articular-hyaluronic-acid-injections-are-safe-and-ef-article-a3856-abstract>

Briefly, 29 studies representing 4,866 unique subjects (US-approved viscosupplement: 2,673, saline: 2,193) were included in this review. Comparing effect sizes before and after treatment, the standardized mean difference (SMD) with US-approved viscosupplements ranged from 1.07 to 1.37 between 4 and 26 weeks, representing very large treatment effects. Comparing these treatment effects to saline controls, SMDs ranged from 0.38-0.43 for knee pain and 0.32-0.34 for knee function during this same timeframe. There were no statistically significant differences between US-approved viscosupplements and saline controls for any safety outcome, including serious adverse events, treatment-related serious adverse events, study withdrawal, and adverse event-related study withdrawal. This meta-analysis concluded that US-approved viscosupplements were safe and efficacious in patients with symptomatic knee osteoarthritis. **We ask that this paper be evaluated and included in all relevant areas of the HTA Final Report.**

A key limitation to all other systematic reviews and meta-analyses on the topic is the inclusion of studies that evaluated viscosupplements not available in the US. The meta-analysis by Miller & Block was extended to compare the safety and effectiveness of US-approved vs. non-US approved viscosupplements. No differences in safety risks were identified; however, the effectiveness of US-approved viscosupplements was notably greater than those not approved in the US. Clearly, any meta-analysis that includes studies of non-US approved viscosupplements will likely underestimate the true treatment effect of viscosupplements available in the US, which are the focus of the HTA.

Key Question 1a (p. 5)

Regarding interpretation of treatment effects from meta-analyses, the standardized mean difference (SMD), or effect size, is a commonly reported statistic. This statistic can be reported in two different contexts: 1) the treatment effect comparing the change from pre-treatment to post-treatment within a single intervention group, and 2) the incremental treatment effect of an intervention above and beyond that of a comparator group.

The use of the effect size statistic to infer clinically meaningful changes in efficacy outcomes is frequently misinterpreted. For example, the control group-corrected treatment effect of viscosupplementation is frequently cited in meta-analyses (Rutjes et al.¹ and others). However, it would be erroneous to estimate clinical relevance or responder rates from this statistic. In order to estimate the clinical benefit to a patient, the pre-treatment to post-treatment effect size in the viscosupplement group, not the placebo-corrected effect size, is the most appropriate statistic. Rutjes et al.¹ report an effect size of 0.37 (corrected for control changes) and then erroneously state that this is equivalent to an improvement in knee pain or function of 0.9 points on a 0 to 10 scale. In fact, Rutjes' reference for this statement² was gleaned from other papers³⁻⁶ that clearly state that pre-treatment to post-treatment treatment effects, not control group-corrected treatment effects, should be used to make this calculation.

The meta-analysis of Miller and Block is the only paper to cite the pre-treatment to post-treatment SMD. Injection of US-approved viscosupplements resulted in an SMD for knee pain of 1.37 (95% CI: 1.12 to 1.61) at 4 to 13 weeks and 1.14 (95% CI: 0.89 to 1.39) at 14 to 26 weeks (both $p < 0.001$). SMDs for knee function were 1.16 (95% CI: 0.99 to 1.34) and 1.07 (95% CI: 0.84 to 1.30), respectively (both $p < 0.001$). These values represent very large treatment effects for viscosupplementation and are independent of the changes reported in saline control groups. Using the assumption that a standardized effect size of 0.37 equates to a 0.9 point improvement (on a 0 to 10 scale) in knee pain or function, the pre-treatment to post-treatment treatment effects for viscosupplementation reported by Miller and Block would be equal to improvements of 2.8 to 3.3 points for knee pain and 2.6 to 2.8 points for knee function (on a 0 to 10 scale). Importantly, the lower-bound confidence limits for all efficacy outcomes (ranging from 0.84 to 1.12) in the Miller & Block meta-analysis are substantially higher than the minimum threshold for clinical importance (0.37). Therefore, it can reasonably be concluded that US-approved viscosupplements result in very large and clinically meaningful improvements in knee pain and function in most patients. We recommend that the interpretation of these data are considered in the HTA Final Report.

Key Question 2 (p. 13)

The safety conclusions of Rutjes et al.¹ are questionable since the association of serious adverse events to the treatment was not established, the safety analysis was heavily influenced by the inclusion of unpublished, unverifiable data, and safety data were analyzed using an odds ratio, a statistic that excludes zero total event trials. Considering that 30 of 38 serious adverse event treatment effects in the meta-analysis of Miller & Block reported zero total events, the odds ratio is arguably an inappropriate statistic for this type of analysis since most data are disregarded.

The findings of the meta-analysis by Miller and Block report no difference in risk between US-approved viscosupplements and saline injection for serious adverse events, treatment-related serious adverse events, subject withdrawals, and adverse event-related subject withdrawals. Additionally, none of the reported serious adverse events were associated with injection of viscosupplement or saline.

Magnitude of Benefit from Other Conservative Therapies (p. 20-21)

The saline-corrected effect size with US-approved viscosupplements ranged from 0.38-0.43 for knee pain and 0.32-0.34 for knee function in the meta-analysis of Miller and Block. Importantly, these effect sizes were realized with no increased safety risks.

The effect sizes reported for other conservative therapies on knee pain (p. 21; excerpted from the OARSI guidelines⁷) and how they compare to viscosupplementation requires further elaboration. As stated in the OARSI guidelines,⁷ there is 100% consensus that optimal management of osteoarthritis requires a combination of non-pharmacological and pharmacological modalities. The effect sizes of selected pharmacological therapies, as reported in the OARSI guidelines, are 0.58 for intra-articular corticosteroid injection, 0.44 for COX-2 inhibitors, 0.29 for NSAIDs, and 0.14 for acetaminophen.

The stated effect size on knee pain for viscosupplementation in the OARSI guidelines is 0.60. The meta-analysis of Miller & Block reported values of 0.38 to 0.43. Regardless, these effect sizes are among the highest reported for pharmacological therapies for knee osteoarthritis. Additionally, viscosupplementation has several distinct benefits compared to other common pharmacological therapies including: a) therapeutic symptom relief for at least 6 months based on the Miller & Block meta-analysis, which is a significantly longer duration of relief than with corticosteroids (generally 2 to 3 weeks⁸); b) injection obviates potential compliance issues associated with oral medications, and c) no serious safety issues were associated with viscosupplements, while COX-2 inhibitors and NSAIDs have clear potential for serious gastrointestinal, renal and/or cardiovascular complications, particularly in older adults and with prolonged use.⁹

Overall, viscosupplementation has the most favorable risk-to-benefit profile of any pharmacological modality for knee osteoarthritis treatment when considering magnitude of therapeutic effect, duration of therapeutic effect, consideration of therapy compliance, and safety risks.

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9. **Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, Knaggs R, Martin D, Sampson L, Schofield P.** Guidance on the management of pain in older people. *Age Ageing.* 2013;42 Suppl 1(i1-57).



To: Shtap@hca.wa.gov; Josh.morse@hca.wa.gov

From: Yvonne Bokelman, Senior Director, Global Market Access, Health Economics & Reimbursement

Phone: 303-741-6590

E-mail: yvonne.bokelman@zimmer.com

Date: September 3, 2013

Subject: Public Comment on Hyaluronic Acid/Viscosupplementation Draft Evidence Report dated August 2, 2013

To HTA Staff:

Zimmer Inc. appreciates this opportunity to publicly comment on the Hyaluronic Acid/Viscosupplementation Draft Evidence Report. We have a number of comments and concerns about how some of the evidence is interpreted in this report, as well as omissions of information and evidence.

The comments contained herein, will be presented in this order: 1) Missing evidence in the draft report; 2) Selective corrections and comments noted by page number; and 3) Clarifying information regarding MCID and the Rutjes article, which as we understand was the basis for re-reviewing HA treatments.

Evidence not included in the Draft Report:

We would like to draw to Hayes and the HTA Committee's attention, two publications that are missing from the analysis in the draft report. First is a publication regarding our product, Gel-One: Effectiveness and Safety of a Multicenter Extension and Retreatment Trial of Gel-200 in Patients with Knee Osteoarthritis *Cartilage October 2012 3: 297-304, first published on July 23, 2012* by V. Strand, et al. The second is an article published in *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders* entitled: US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials, and published on-line on September 2, 2013.

Additionally, it was noted on page 18 of the draft evidence report that Group Health and Regence BCBS did not have relevant coverage policies related to viscosupplementation or HA injections. We would like to point out that both payers have policies and guidelines that support the use of HA injections. Regence BCBS medication policy #dru275 addresses coverage for Gel-One, and has been in place since 2012, and similar policies exist for other HA products. The policy pdf is included with this comment letter. In addition for Group Health, HA coverage is denoted on the "Office-Administered Prior Authorization Drug List" dated June 25, 2013. In addition, while it is true there is no national coverage policy from CMS, viscosupplementation is covered by all Medicare Administrative Contractors for Medicare beneficiaries, and a few do have specific LCDs or guidelines, usually noted under Hyaluronate Polymers.

Examples include Palmetto, Novitas and FCSO.

Specific Draft Evidence Report Comments:

We would like to bring to Hayes and the HTA Committee's attention, some clarifications and comments in regard to the draft evidence report.

Page 1: **Summary of Background and Technology Description**, Paragraph 4. In the second to last sentence in the paragraph it is questioned whether *hylan* is also used to refer to Gel-One. It is not. "Hylan" is specific to the Synvisc product. This is true through-out the report, wherever "hylan" is noted.

Page 2: Policy Context, paragraph 2 reporting conclusions in the 2010 Washington HTA report. The definition of the minimal clinical importance is being misapplied. Please see further details regarding this later in this comment letter. Further, noting that "eventual recovery of function is uncertain", it should be noted that HA is not used, nor approved to treat or modify the underlying disease state of osteoarthritis, but rather for relief of symptomatic OA knee pain. And, as noted above, hylan refers only to the HA polymer comprising Synvisc.

In paragraph three of this section, the conclusion that there are serious safety concerns based on the Rutjes article is inappropriate due to the poor quality of the data and the flawed methodologies. This will be addressed in the last section of this letter. And, finally, it is noted that the "American College of Radiology" has issued guidelines in the last sentence of the paragraph. This should be corrected to reflect the American College of Rheumatology.

Page 5: **Findings** - In previous comments in an attempt to offer suggestions and clarifications with regard to the draft questions, with question 1A, we would again offer that viscosupplementation is not indicated as a treatment for osteoarthritis, but rather provides pain relief for osteoarthritis. We are concerned that the data may be misinterpreted as to HA's efficacy (as referenced on Page 19, paragraph 1) with regard to the recovery of function, when HA injections are indicated for pain relief.

Page 6: Paragraphs 4 and 5 referencing trial results regarding responder rates and loss of follow-up: At least for the study of Gel-One, we found that the responder rate in our study was considerably higher than that which is reported in paragraph 4 using OMERACT-OARSI responder criteria. In paragraph 5, the high loss of follow-up provides a generalized negative connotation which again was not the experience in the Gel-One study.

Page 11: In paragraph 2, there is a suggestion of no difference between FDA and non-FDA approved products. We disagree with that statement, and believe that there is a difference when studying US versus OUS products. This is evidenced in the results of the meta-analysis published in *Clinical Medicine Insights* noted above.

Page 14: In Table 2, **Summary of Findings** regarding Adverse Events, a reminder again that "hylan" refers to one specific HA product. In addition, as noted earlier, relatedness to treatment is not addressed; gastrointestinal, cardiac, and cancer events have never been shown to be caused by or related to HA treatment.

Page 15: The two case series reports on long term results are for "hylan" only.

Page 16: Question #3, paragraph 1: We would agree with the findings that there is an opportunity for more studies to help specify the ideal candidates for HA treatment

relative to the subpopulations of patients noted. However at this time, due to the overall safety and efficacy of US-approved products, there is very little patient risk, and HA treatments provide a significant non-surgical pain relief alternative and should continue to be offered as the clinical science is even more fully developed.

Page 19: **Overall Summary and Discussion**, paragraph 1, second sentence referencing the benefit may be too small. The IMMPACT guideline was previously referenced in the draft report. IMMPACT criteria is 10mm improvement from baseline. All pertinent studies show at least a 10mm baseline for US approved products.

Furthermore, the conclusion statement regarding physical function in the fourth sentence validates our concern noted above from page 5 as well. Again, specifically we note that viscosupplementation is not indicated as a treatment for osteoarthritis, but rather provides pain relief for osteoarthritis.

In the second paragraph, second sentence we would go a step further, not only is the relationship between systemic events and HA injections unclear, we believe no connection has been established at all.

Page 20: Other Considerations, last paragraph on the page, suggesting MCID for “understanding group differences” in trials is inappropriate, per Dr. Dworkin. This is where the area of conflict developed with the AAOS Clinical Practice Guidelines, and the inappropriate application of MCID. Dr. Dworkin appeared before members of the CPG Committee to try to explain and redirect them on the appropriate use of MCID, which specifically is not using MCID/MCII to compare groups.

Page 24: **Technology Description**, first paragraph, second to last sentence, again, “hylan” is not also used to refer to Gel-One. In the third paragraph, fourth sentence regarding systemic effects, again, not all effects noted have been demonstrated to be specifically related to the HA treatment.

Page 34: Under **Pain**, and in the fourth bullet point, the third sentence about IMMPACT contradicts the draft evidence report’s earlier discussion about MCID.

Page 38: In the table of studies, again Gel-One is being noted as “hylan”, which is incorrect.

Further Comments regarding MCID and the Rutjes publication:

MCID: Zimmer is concerned with Hayes interpretation and use of MCID. Similarly we raised these same concerns with AAOS with regard to the development of their Clinical Practice Guidelines. Our issue is how the MCII or MCID Effectiveness Measure is defined and used for an assessment of clinical importance for patients with symptomatic osteoarthritis of the knee. This should also be viewed in the context that all meta-analysis results as reviewed in particular by AAOS showed statistically significant treatment effects across WOMAC pain, function and stiffness subscales scores. The following bullets explain the concerns with MCII/MCID:

- It is vital to good science that measurement instruments must be applied to the same scientific context in which the measurement instrument was originally defined.
- MCII/MCID measures have been derived from within-group patient data and defined with respect to baseline at the individual patient level.
- This means that the MCID measure that is used in the draft evidence report should only be applied to the assessment of clinical importance for change from baseline for each patient. However, the reference of MCID is being used for the assessment of clinical

importance for group differences in change from baseline between the treatment and placebo groups.

- There has been substantial discussion of incorrect usage of the MCII/MCID measures some of which has been used by manufacturers in convincing the FDA to correctly apply these measures. Some important references include:
 - Togo et al. (2011) [Ref. 1] distinguishes minimal clinically important change from baseline from minimal clinically important difference between groups
 - Dworkin et al. (2009) [Ref.2], as made in IMMPACT recommendation, states that “it is crucial to recognize that criteria for clinically important changes in individual cannot be extrapolated to the evaluation of group differences.” The conclusion is that “given their critical differences, evaluation of the clinical meaningfulness of group difference in chronic pain trials should not be based on criteria for evaluating clinically meaningful changes in individual patients.”
 - Dr. Marc Hochberg stated in response to a question from a medical reviewer at CDRH during the FDA-sponsored public meeting on MCID in 2012 [Ref.3], that a measure of minimal clinical importance determined at the individual level is meant for the purposes of determining the proportion of subjects who meet the standard in order to be able to compare that between treatment groups and it is not intended to be used to interpret group differences as to whether it exceeds or fails to exceed that measure in making decision from a regulatory standpoint. As one of the researchers who developed the MCII measures, Dr. Hochberg’s statement on proper use and interpretation should be taken as important guidance.
- The confusion over these methodologies and acronyms may have led FDA to remove all references to minimum important difference or minimum clinically important differences in the latest FDA guidance (issued in Dec. 2009) [Ref. 4] on patient reported outcome measures, a point duly noted by Dr. Kathleen Wyrwich during the FDA-sponsored public meeting on MCID in 2012 [Ref.3].
- At this time we are not aware of any validated study to determine the minimum clinically important differences between groups and believe that any such definition must abide by sound scientific principle such as those espoused in the IMMPACT recommendation.
- Chuang-Stein et al. (2010) [Ref. 5] argues that the most reasonable role for a minimum clinically important difference between groups measure is to use it as a target sample size and power calculation during study design, while cautioning against overuse and over-interpretation of the concept.

References:

1. Togo K, Matsuoka N, Hashigaki S, Imai K, Moriya T. Clinically important effects in new drug development. *Drug Information Journal*. 2011; Vol. 45, pp 805-810.
2. Dworkin RH et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009; Vol. 146, 238-244.
3. Public transcript from “Minimum Clinically Important Difference (MCID): Defining Outcome Metrics for Orthopedic Devices – Public Meeting”, held at FDA White Oak Campus on Nov 27-28, 2012.
4. US Department of Health and Human Services, FDA, CDER, CBER, CDRH. Guidance for industry, patient-reported outcome measures: use in medical product development to support labeling claims. Dec 2009.
5. Chuang-Stein C, Kirby S, Hirsch I, Atkinson G. The role of the minimum clinically important difference and its impact on designing a trial. *Pharmaceutical Statistics*. 2011; Vol. 10, 250-256.

With regard to the Rutjes article, which again seemed to prompt this re-review by Washington State HTA, we would offer the following concerns about that publication:

- The meta-analysis included published, non-published, non-peer-reviewed, and conference

proceedings.

- Many studies included were conducted outside of the US and concerned products not approved for use in the US.
- In order to estimate the clinical benefit to a patient, the pre-treatment to post-treatment effect size in the viscosupplement group, not the placebo-corrected effect size, is the most appropriate statistic. Rutjes et al.¹ report an effect size of 0.37 (corrected for control changes) and then erroneously state that this is equivalent to an improvement in knee pain or function of 0.9 points on a 0 to 10 scale. In fact, Rutjes' reference for this statement was gleaned from other papers that clearly state that pre-treatment to post-treatment treatment effects, not control group-corrected treatment effects, should be used to make this calculation.
- The inappropriateness in Rutjes is that the concept of a 0.9 point improvement as clinically meaningful threshold for knee pain severity in OA patients is based on pre to post improvement values, not control-corrected improvements. Rutjes utilized the control-corrected effect size and erroneously estimated clinical meaningfulness. Clinical meaningfulness cannot be estimated by this statistic, rather only from a pre to post effect size. To be clear, the comparison should have been within patient or within treatment group while Rutjes makes it between groups.
- We believe that in the Rutjes article, the methods were flawed, the data was poor quality, and the flawed results only marginally support a conclusion that the authors proceed to overstate rather severely. In particular, the characterization of significantly increased safety risks is problematic in light of the generally incomplete safety data amongst the Rutjes source data and the failure to account for or include information regarding adverse event causality determinations.

Summary:

In our opening comments above, we noted a new publication in *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, entitled: US-approved Intra-articular Hyaluronic Acid Injections are Safe and Effective in Patients with Knee Osteoarthritis: Systematic Review and Meta-analysis of Randomized, Saline-controlled Trials. This meta-analysis is the only paper to cite the pre-treatment to post-treatment Standardized Mean Difference (SMD). The values reported represent very large treatment effects for viscosupplementation and are independent of the changes reported in saline control groups. Using the assumption that a standardized effect size of 0.37 equates to a 0.9 point improvement (on a 0 to 10 scale) in knee pain or function, the pre-treatment to post-treatment treatment effects for viscosupplementation reported would be equal to improvements of 2.8 to 3.3 points for knee pain and 2.6 to 2.8 points for knee function (on a 0 to 10 scale). With this newly updated meta-analysis, it can therefore, be reasonably concluded that US-approved viscosupplements result in very large and clinically meaningful improvements in knee pain and function in most patients. We recommend that the interpretation of these data be considered by Hayes and the HTA Committee, in addition to the numerous other comments above.

Most importantly, we request that the WA State HTA Committee maintain a position of positive coverage for HA/Viscosupplementation, allowing a safe and efficacious pain-relief option for the State-insured beneficiaries. To do anything less, would create a coverage environment in the State of Washington, where State-insured beneficiaries potentially receive less care, or certainly less alternatives than other insured citizens of the State, and those insured in federal programs.

Zimmer appreciates the opportunity to provide comments on this draft evidence report, and looks forward to the updated information, analysis and discussion.

Masters, Christine V. (HCA)

From: Alan Ramsey <alramsey1@yahoo.com>
Sent: Saturday, October 05, 2013 9:06 AM
To: Teresa Rogstad
Cc: Sue Levine
Subject: Re: Medical Review, Report for State of WA on Viscosupplementation
Attachments: Hayes_HA-Visco_Final Report_9-23-13_Medical_Review.docx

Hi Teresa,

The report is very well written and easy to follow from my standpoint. The MCID issue made perfect sense to me as well. I had only a few minor comments/suggestions. Hope they help,

Alan

From: Teresa Rogstad <trogstad@hayesinc.com>
To: Alan Ramsey <alramsey1@yahoo.com>
Cc: Sue Levine <slevine@hayesinc.com>
Sent: Thursday, September 26, 2013 3:18 PM
Subject: Medical Review, Report for State of WA on Viscosupplementation

Greetings, Dr. Ramsey. As you probably recall, Hayes is currently under contract with the State of Washington to prepare HTAs for the state's public HTA Program, and I have another one I would like to ask you to review.

The attached report is an update of a report that we prepared for Washington 3 years ago. I had assumed that medical review was not necessary since it is an update report. However, the Program Director informed me today that he does want there to be a physician review of the report.

Would it be possible for you to review the report and return it to me by **Monday, October 7**? If not, how soon would you be able to review it? I apologize for this short notice.

The thorniest issue with this report is the controversy and varying definitions of MCID/clinical response and the distinction between within-group improvement from baseline and a between-group difference. If what I have written on these issues does not make sense to you, please let me know.

Terry

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