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Intra-Articular Viscosupplementation With Hylan G-F 20 To Treat Osteoarthritis of the Knee

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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Executive Summary

Objective

To assess the effectiveness and cost-effectiveness of hylan G-F 20 as a substitute for existing treatments for pain due to osteoarthritis (OA) of the knee, other viscosupplementation devices, and/or as an adjunct to conventional therapy.

Hylan G-F 20 (brand name Synvisc, which is manufactured by Genzyme) is a high molecular weight derivative of hyaluronan, a component of joint synovial fluid. It acts as a lubricant and shock absorber. It is administered by injection into the joint space to treat pain associated with OA of the knee. Although the injection procedure is an insured service in Ontario, the device, hylan G-F 20, is not.

Clinical Need

Osteoarthritis is prevalent in 10% to 12% of Ontario adults, and exceeds 40% in Ontario residents aged 65 years and older. About one-half of these people have mild, moderate, or severe OA of the knee. Conventional treatment involves a combination of nonpharmacological management (e.g., weight loss, exercise, social support, and patient education), drugs, (e.g., acetaminophen, COX-2 inhibitors, nonsteroidal anti-inflammatory drugs with/without misoprostol, intra-articular glucocorticoids, opioids, and topical analgesics) and surgical interventions, such as debridement and total knee replacement, when pharmacological management fails.

The growing burden of OA of the knee in the aging Ontario population combined with recent safety concerns about COX-2 inhibitors and long wait times for total joint replacement is placing pressure on the demand for new, effective technologies to manage the pain of OA.

The Technology

Hylan G-F 20 is derived from rooster comb hyaluronan (HA). At the time of writing, eight viscosupplement hyaluronic products are licensed in Canada. Hylan G-F 20 is distinguished from the other products by its chemical structure (i.e., cross-linked hyaluronan, hence hylan) and relatively higher molecular weight, which may bestow greater therapeutic viscoelastic properties. A complete treatment cycle of hylan G-F 20 involves an intra-articular injection of 2 ml of hylan G-F 20 once a week for 3 weeks. It is licensed for use for patients in all stages of joint pathology, but should not be used in infected or severely inflamed joints, in joints with large effusion, in patients that have skin diseases or infections in the area of the injection site, or in patients with venous stasis. It is also contraindicated in patients with hypersensitivities to avian proteins.

Review Strategy

The Medical Advisory Secretariat used its standard search protocol to review the literature for evidence on the effectiveness of intra-articular hylan G-F 20 compared with placebo, as a substitute for alternate active treatments, or as an adjunct to conventional care for treatment of the pain of OA of the knee. All English-language journal articles and reviews with clearly described designs and methods (i.e., those sufficient to assign a Jadad score to) published or released between 1966 and February 2005 were included. Two more recently published meta-analyses were also included. The databases searched were Ovid MEDLINE, EMBASE, the Cochrane database and leading international organizations for health technology assessments, including the International Network of Agencies for Health Technology

Assessments .The search terms were as follows: hyaluronan, hyaluronate adj sodium, hylan, hylan G-F 20 (Synvisc), Synvisc, Hyalgan, Orthovisc, Supartz, Artz, Artzal, BioHY, NASHA, NRD101, viscosupplementation, osteoarthritis, knee, knee joint. The primary outcome of interest was a clinically significant difference, defined as greater than 10 mm on 100 mm visual analogue scale, or a change from baseline of more than 20% in the mean magnitude of pain relief experienced among patients treated with hylan G-F 20 compared with those treated with the control intervention.

One clinical epidemiologist reviewed the full-text reports and extracted data using an extraction form. Key variables included, but were not limited to, the characteristics of the patients, method of randomization, type of control intervention, outcome measures for effectiveness and safety, and length of follow-up. The quality of the studies and level of the evidence was initially scored by one clinical epidemiologist using the Jadad scale and GRADE approach. Level of quality depends on the amount of certainty about the magnitude of effect and is based on study designs, extent of methodological limitations, consistency of results and applicability (i.e. directness) to the Ontario clinical context. The GRADE approach also permits comment on the strength of recommendations resulting from the evidence, based on estimates of the magnitude of effect relative to the magnitude of risk and burden and the level of certainty around these estimates. The quality assessments were subsequently peer-reviewed.

Summary of Findings

The literature search revealed 2 previous health technology assessments, 3 meta-analyses of placebo-controlled trials, 1 Cochrane review and meta-analysis encompassing 18 randomized controlled trials (RCTs) that compared hylan G-F 20 to either placebo or active treatments, 11 RCTs of hylan G-F 20 (all included in the Cochrane review), and 10 observational studies. Given the preponderance of evidence, the Medical Advisory Secretariat's analysis focused on studies with Level 1 evidence of effectiveness (i.e., the meta-analyses of RCTs and the RCTs). Only safety data from the observational studies were included.

The authors of the 2 health technology assessments concluded that the data were sparse and poor quality. There was some evidence that hylan G-F 20 delivered a small, clinical benefit at 3 to 6 months after treatment on a magnitude comparable to NSAIDs and intra-articular steroids. Hylan G-F 20 appeared to carry a risk of a local adverse reaction of in the range of 3% to 18% per 100 injections, but there was no apparent risk of a severe adverse event, although the data were limited.

Each of the 3 meta-analyses of placebo-controlled trials of intra-articular hyaluronans had only 3 trials involving hylan G-F 20. There results were inconsistent, with one study concluding that intra-articular hyaluronans were efficacious, whereas the 2 other analyses concluded the effect size was small (0.32) and probably not clinically significant. The risk of a minor adverse event ranged from 8% to 19% per 100 injections. Major adverse events were rare.

The authors of the Cochrane review concluded that a pooled analysis supported the efficacy of hyaluronans, including hylan G-F 20. The 5- to 13-week post-injection period showed an improvement from baseline of 11% to 54% for pain and 9% to 15% for function. Comparable efficacy was noted against NSAIDs, and longer-term benefits were noted in against steroids. Few adverse events were noted.

When the Medical Advisory Secretariat applied the criterion of clinical significance to the magnitude of pain relief reported in the RCTs on hylan G-F 20, the following was noted:

- There was inconsistent evidence that hylan G-F 20 was clinically superior to placebo at 5 to 26 weeks after treatment.
- There was consistent evidence that, in terms of delivering pain relief, hylan G-F 20 was no better or worse than NSAIDs or intra-articular steroids at 5 to 26 weeks after treatment.

- There was consistent evidence that hylan G-F 20 was not clinically superior to other hyaluronic products.
- There was consistent evidence that hylan G-F 20 delivered a small magnitude of clinical benefit at 12 to 52 weeks post-injection when administered as an adjunct to conventional care.

There were limitations to the methods in many of the RCTs involving hylan G-F 20. When only the results from the higher-quality studies were considered, there was level 2 evidence that hylan G-F 20 was not clinically superior to placebo (or another hyaluronan) at 1 to 26 weeks after treatment in older patients with advanced disease for whom total knee replacement was indicated. There was level 2 evidence that hylan G-F 2- was comparable to NSAIDs at 4 to 13 weeks after treatment, and level 2 evidence that hylan G-F 20 was superior to placebo as an adjunct to conventional care 4 to 26 weeks after treatment.

With respect to safety, overall, hylan G-F 20 carries a risk of a minor, local adverse event rate of about 8% to 19% per 100 injections. Incidents of moderate-severe post-injection inflammatory joint reactions have been reported, but the likelihood appears to be low (0.15% of patients).

Economic Analysis

Case-costing estimates suggest that the annual cost of 2 treatment cycles of hylan G-F 20 (plus analgesics for breakthrough pain) is almost equivalent to the annual cost of taking a NSAID (with a gastroprotective agent) and is more expensive that taking intra-articular corticosteroids (plus analgesics for breakthrough pain). The estimated cost of funding hylan G-F 20 as an adjunct to conventional therapy (i.e., any of analgesics, NSAIDs, intra-articular steroids, physiotherapy, and surgery) is $700 per patient per year. Given the huge burden of mild to moderate OA among adults who seek medical care for it in Ontario (about 300,000), funding hylan G-F 20 as an adjunct to existing treatment could be expensive, depending on its diffusion and uptake. If only 10% to 30% of patients choose this option, then the estimated budget impact would be $21 million to $63 million (Cdn) per year.

Conclusions

When the benefits relative to the risks and costs are considered, NSAIDs and hylan G-F 20 appear comparable, as the table shows. Consequently, there's little evidence on which to recommend hylan G-F 20 over NSAIDs, except perhaps for patients who cannot tolerate NSAIDs, although this evidence is indirect, since no studies looked specifically at this population.

Comparison*	Magnitude of Benefit	Risk	Cost-burden	Quality	Strength
NSAIDs	Equivalent	Low	Equivalent	Moderate	Weak
IA steroids	Equivalent	Low	More costly	Moderate	Strong
Other hyaluronans	Equivalent	Low	Equivalent	Low	Weak
Adjunct to CC	Better	Low	More costly	Moderate	Weak

*CC indicates conventional care; IA, intra-articular; NSAID, nonsteroidal anti-inflammatory drug.

Intra-articular steroids appear to deliver the same risks and clinical benefits as hylan G-F 20 at a lower cost; therefore, there's evidence that intra-articular steroids are the preferred option. Hylan G-F 20 as an adjunct to conventional care appears to deliver some clinical benefit, although funding hylan G-F 20 as an adjunct would have considerable budget impact, so the benefits of this option do not clearly outweigh the costs. There's some uncertainty about the effect of hylan G-F 20 relative to other hyaluronans, mostly because some of the trials of this comparison were not published.

Many of the studies of hylan G-F 20 have considerable methodological limitations that result in

uncertainty about the magnitude of effect. An upcoming review of the evidence by the Osteoarthritis Advisory Panel of clinical experts will likely help to reduce some of this uncertainty.

There is moderate evidence that hylan G-F 20 is no more clinically effective than NSAIDs. The evidence that hylan G-F 20 might be an appropriate option for a person with OA of the knee who cannot tolerate NSAIDs is indirect. The possible benefit of fewer cases of NSAID-induced gastropathy in this population must be weighed against the uncertainty of a severe inflammatory adverse reaction to hylan G-F 20.

Similarly, there is moderate evidence that hylan G-F 20 is no more clinically effective than intra-articular corticosteroids. The lower cost of intra-articular corticosteroids makes them the preferred option.

There is moderate evidence that hylan G-F 20 is effective as an adjunct to conventional care, delivering a small magnitude of temporary relief at 4 to 26 weeks after treatment. The estimated additional cost to the system of providing hylan G-F 20 as an adjunct to conventional care is about $700 (Cdn) per patient annually. The magnitude and duration of clinical benefit of hylan G-F 20 must be weighed against the uncertainty and potential magnitude of the budget impact (about $35 million to $105 million (Cdn) per year) of funding this device given the high burden of OA in Ontario adults.

There is level 2 evidence that hylan G-F 20 is not effective in people with advanced OA for whom total knee replacement is indicated.

Abbreviations

AC	Appropriate care
CAHTA	Catalan Agency for Health Technology Assessment
CI	Confidence interval
COX-2	Cyclooxygenase-2
HA	Hyaluronan
IA	Intra-articular
IA HA	Intra-articular hyaluronan
MCID	Minimal clinically important difference
MSAC	Medical Services Advisory Committee (Australia)
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatology
QALY	Quality adjusted life year
RCT	Randomized controlled trial
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WMD	Weighted mean difference

Objective

To assess the effectiveness and cost-effectiveness of hylan G-F 20 as a substitute for existing treatments for pain due to osteoarthritis (OA) of the knee, other viscosupplementation devices, and/or as an adjunct to conventional therapy

Hylan G-F 20 (brand name Synvisc) is a high molecular weight derivative of hyaluronan, a component of synovial fluid, which is found in the joints and acts as a lubricant and shock absorber. It is administered by injection into the joint space (i.e. viscosupplementation) to treat pain associated with OA of the knee. Although the injection procedure is an insured service in Ontario, the device, hylan G-F 20, is not.

Background

Clinical Need: Target Population and Condition

Osteoarthritis is a chronic, degenerative disease caused by deteriorating cartilage in one or more joints. It leads to joint damage, pain, and stiffness. The most commonly affected joints are the knees, hips, hands, feet, and spine. Major risk factors for OA are genetic predisposition, age, gender, obesity, joint trauma, and joint overuse.

The prevalence of OA is 10% to 12% in the Ontario adult population.(1) It exceeds 40% in Ontario residents aged 65 years and older. About one-half of these people have mild, moderate, or severe OA of the knee. The burden of this disease on quality of life, disability, and health care utilization is high. According to the 2003 Arthritis in Canada Report, (2) people aged 45 to 65 years with arthritis (most of whom have OA) were more likely than others of this age with other chronic diseases to have moderate to severe pain (35% vs. 12%). They were also more likely to have activity limitations (52% vs. 28%), take pain relievers and anti-inflammatory drugs (79% vs. 66%), and have visited a primary care physician at least 4 times in the previous year (44% vs. 32%). In 2000/2001, compared with people with other chronic conditions, those with arthritis made more OHIP claims on average for professional (47 vs. 28) and laboratory services (32 vs. 20), and had over twice the rates per 1000 people of same-day surgery (430 vs. 210) and in-patient hospital utilization (400 vs. 180). (1)

There is no cure for OA. The goals of treatment are to reduce joint pain, improve joint mobility, and limit functional impairment. Current guidelines (3) based on evidence and expert opinion outline a complementary approach to treatment that involves the following:

- Non-pharmacological management (e.g., weight loss, exercise, social support, and patient education);
- Drugs (e.g., acetaminophen, COX-2 inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) plus misoprostol, intra-articular glucocorticoids, opioids and topical analgesics); and
- Surgical interventions when pharmacological management fails.

NSAIDs carry an established risk of gastrointestinal toxicity that can cause gastrointestinal bleeding. (4) Selective NSAIDs, known as COX-2 inhibitors (e.g., celecoxib, rofecoxib), which reduce the risk of gastrointestinal bleeding by selectively inhibiting certain inflammatory enzymes while sparing gastroprotective ones, were introduced in 1999 and 2000. (5) They rapidly became the favoured alternative for managing the pain of arthritis in people at risk of NSAID-induced gastropathy (those aged

65 years or older, with comorbid medical conditions, with concomitant use of anticoagulants or oral glucocorticoids, with a history of peptic ulcer or an upper gastrointestinal bleed). (4;6) The number of prescriptions written for COX-2 inhibitors in Ontario increased by 224% between 1999 and 2001. In 2001, more than 844,000 prescriptions were written for those aged 65 years and older, at a cost of $46,116,772 (Cdn**)** to the Ontario government. (1)

However, data from clinical trials (5;7;8) that found a higher rate of cardiovascular events (including heart attack and stroke) among participants treated with COX-2 inhibitors raised concerns about the safety of this class of drugs In 2004 Merck & Co. Inc. withdrew rofecoxib (brand name Vioxx) from the worldwide market. In April 2005, after a review of information, Health Canada asked Pfizer to suspend sales of its drug bextra (valdecoxib) because of safety concerns and placed new restrictions on the use of Celebrex (celecoxib). Consequently, an estimated 30,000 to 40,000 Ontario residents have stopped taking COX-2 inhibitors over the past year, most of whom have OA.

Moreover, similar concerns have been raised about some nonspecific NSAIDs, in particular, naproxen. In December 2004, the American National Institute of Aging suspended the use of naproxen in a large, national Alzheimer disease prevention trial after preliminary data showed there was some evidence of increased risk of cardiovascular events, when compared to placebo, for patients taking naproxen. Consequently Health Canada has committed to undertake a review of the safety of nonspecific NSAIDs. At the time of writing, the results and implications of this review are pending.

Patients with severe symptomatic OA that has failed to respond to medical therapy are referred to an orthopedic surgeon. Surgical options range from arthroscopic debridement and osteotomy to unicompartmental or total joint replacement. Arthroscopic knee surgery accounted for nearly one-half of the 44,000 arthritis-related surgical procedures in Ontario in 2001/2002. (1) The most common type of knee arthroscopic procedure was debridement. Total joint arthroplasty is generally considered the definitive treatment for OA of the knee. In 2001, more than 11,000 total knee replacements were performed in Canada. (1) According to the total joint replacement registry data, an estimated 8000 Ontario residents are waiting for total joint replacement surgery. According to data in the Ontario Joint Replacement registry, (9) the median wait time from decision to surgery was 106 days. The high prevalence and growing burden of OA of the knee in an aging Ontario population, combined with recent safety concerns about COX-2 inhibitors and long wait times to receive total joint replacement surgery, is increasing demand for new, effective technologies to manage the pain of OA.

Measuring the pain of osteoarthritis

The primary indication for the use of hylan G-F 20 is pain, so the primary outcome of interest is the magnitude of reduction of pain reported by patients who receive the technology. The OMERACT (Outcome Measures in Rheumatology) initiative is an informal, international network of working groups and gatherings interested in outcome measurement across the spectrum of rheumatology intervention studies. OMERACT meetings are held every 2 years to develop new consensus and guidelines for outcomes in rheumatic diseases. In 1997, the OMERACT participants agreed on a core set of 4 domains for outcome measurement in future Phase III clinical trials of OA of the hip, knee, and hand: pain, physical function, patient's global assessment, and, for studies of at least 1 year, joint imaging. (10) They also agreed that it was not necessary to specify exact instruments to measure these domains, but that any instrument used should be of adequate reliability, validity, and responsiveness. The 2 most common disease-specific instruments used to measure OA treatment outcomes are the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (11) and the Lequesne Index. (12) (See Appendix 1 for fuller descriptions.)

The WOMAC (Table 1) is the most widely used and best-proven condition-specific health assessment

instrument for patients with OA of the lower extremities. It has 24 items that measure 5 dimensions of pain, 2 of stiffness, and 17 of physical function. The scales for each dimension may be ordinal, based on a Likert scale (0–4) scale ranging from 0 ("no symptoms") to 4 ("extreme symptoms"), or continuous, using a visual analogue scale. It can be scored in a number of ways, including the total sum out of 96, or by the mean ordinal or continuous score for each item or dimension.

The Lequesne index is a composite scale that was developed in France and is used primarily in Europe. It has 11 questions subdivided into 3 sections: pain, maximum distance walked, and activities of daily living. The first section asks 5 questions about pain; the second, 2 questions on the distance someone is able to walk with or without crutches; the third, 4 questions on the ability to manage stairs, walk, and squat. Another common tool is the visual analogue scale; patients report pain intensity on a continuous scale of 0 mm to 100 mm or sometimes 1cm to 10cm.

Table 1: Osteoarthritis-Specific Health Assessment Instruments

Instrument Scale*	Interpretation
WOMAC-A (Pain), 5 items: 20 WOMAC-B (Stiffness), 2 items: 8 WOMAC-C (Function), 17 items: 68 Total score: 96	0: no symptoms 96: maximum symptoms Individual items can be scored on various scales: 0–4 Likert, 0–10 ordinal, 0–100 VAS, where 0 is no symptoms
Lequesne Pain: 8 Distance: 8 Activities: 8 Total: 24	0: no symptoms 24: maximum symptoms Sometimes the response is plotted on a curve and the area under the curve is integrated and interpreted.
VAS 10-point scale	0: no pain; 10: extreme pain
VAS 100 mm	0: no pain; 100: extreme pain

*WOMAC indicates Western Ontario and McMaster Universities Osteoarthritis Index; VAS, visual analogue scale.

Many studies report statistically detectable differences in pain scales without considering the clinical importance of these differences. The minimal clinically important difference (MCID) (Table 2) is the smallest difference in score (i.e., the effect) that patients perceive as beneficial. This threshold seems to vary by disease process and type of chronic pain experienced by the patient. For OA pain, 2 studies that attempted to correlate the magnitude of change on a VAS scale with a patient's perception of the improvement in the pain of OA derived similar estimates of the MCID.

Angst and colleagues (13) compared differences on the continuous WOMAC numerical rating scale from 0 to 100 with patients' reported assessments. They concluded that a change of 8 to 10, consistent with a 17% to 22% change from baseline, correlated with patients' reporting that they were "slightly better." Similarly Ehrich and colleagues (14) compared the global response to therapy of patients with OA to changes on the WOMAC VAS scores for pain and concluded that mean changes of 9 to 12 mm on a 100 mm VAS were the smallest that patients with hip and knee arthritis could perceive. For this review, an absolute reduction in the 100 mm VAS scale for pain of less than 10 mm or a change in baseline score of less than 20% was interpreted as clinically insignificant.

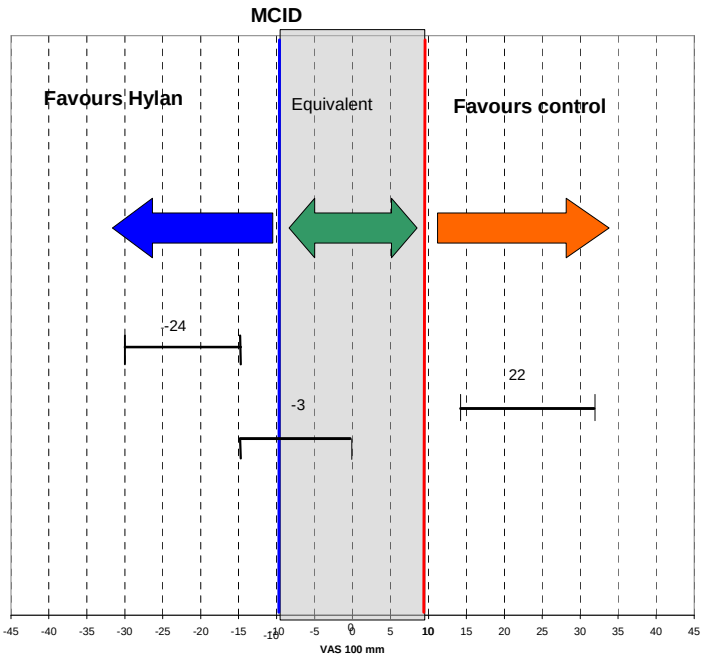
Table 2: Minimal Clinically Important Differences

Absolute Change on the 100 mm VAS*	Absolute Change on the Likert Scale (0 to 4)	Reduction From Baseline, %	Patient's Perception of Pain
10mm	0.4	20	Slightly better

*VAS indicates visual analogue scale.

Outcome pain measures in clinical trials can indicate either the magnitude of change from baseline or the magnitude of difference in final scores between treatment and control arms. They are often summarized as the weighted mean difference (WMD), which describes magnitude of change in terms of the VAS, or the standardized mean difference (SMD), which describes the difference in terms of the standard deviation. The SMD is also called the effect size. An effect size of 0.0 to 0.5 is considered small; from 0.5 to 0.8, moderate; and above 0.8, large. (15) For more on these summary measures, see Appendix 1.

Figure 1: Identifying Differences in Outcome Pain Scores* Between Treatment and Control Groups That Exceed the Minimally Clinically Important Difference



*Using the 100 mm visual analogue scale.

In the above example (Figure 1), the 95% confidence interval (CI) of the point estimate -24 clearly exceeds the MCID threshold. This means that one can conclude that the mean magnitude of reduction in pain experienced by the group treated with the intervention of interest is clinically significant compared with the magnitude of pain reduction experienced by the group with the control intervention. The 95% CI of the -3 point estimate falls within the equivalent zone, which suggests that the treatment of interest might not be better than the control intervention. The Cl surrounding the 22-point estimate falls within the zone that suggests the control intervention is clinically superior to the treatment in reducing pain.

Existing Treatments for Pain Due to Osteoarthritis of the Knee

Table 3: Relevant Comparators for the Treatment of Osteoarthritis of the Knee

Conventional non-surgical treatments for osteoarthritis joint pain according to guidelines	
Treatment	**Comment**
Acetaminophen	First-line, according to Ontario guidelines. A recent Cochrane review (16)concluded that acetaminophen was superior to placebo. The number of people needed to treat to achieve an improvement in pain was 2.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Second-line, according to Ontario guidelines, although a recent meta-analysis (17) and Cochrane review (18)concluded that NSAIDs are statistically superior to acetaminophen in reducing hip and knee pain, although the size of the effect was modest. Discontinuation rates due to adverse events were not statistically significant between NSAID- and acetaminophen-treated groups. A recent Cochrane review found that no substantial evidence is available related to efficacy to distinguish between equivalent recommended doses of NSAIDs. (19)
Selective COX-2 inhibitors	Under review in light of recent evidence that long-term use of this class of drugs increases the risk of heart attack and stroke. (8)
Opioids	Effective, but adverse events include nausea and constipation. (20)
Intra-articulator corticosteroid injections	A recent Cochrane review (21) concluded that IA corticosteroid was more effective than IA placebo for pain reduction (WMD, -17.79; 95% CI, -25.02 to -10.55). There was evidence of effectiveness for up to 4 weeks after treatment, but at 4 to 24 weeks, there was no evidence that they had an effect on pain.
Topical pharmaceuticals	Evolving evidence suggests a modest effect. (22;23)
Intra-articular low molecular weight hyaluronan	Inconsistent evidence, although a recent Cochrane review (24) concluded that hyaluronan products in general appear superior to placebo, but that there is considerable heterogeneity in clinical response and differential therapeutic effects by different HA products.

New Technology Being Reviewed: Hylan G-F 20

Hylan G-F 20 is derived from hyaluronan, a large, linear glycosaminoglycan that is a natural part of the synovial fluid found in joint cavities. Hyaluronan has unique viscoelastic properties, which means it behaves as a viscous liquid at low shear rates and as an elastic solid at high shear rates. This enables the joint fluid to act as a viscous lubricant during slow movements of the joint and as an elastic shock absorber during rapid movements. Hyaluronan might also play a role in modulating inflammatory mechanisms and cartilage production as well as the flow of fluid through the joint. (25) In OA, the concentration and molecular weight of synovial fluid hyaluronan are reduced, and the viscoelastic properties of the fluid are compromised. The original rationale for the use of intra-articular hyaluronan to treat pain due to OA was to increase the viscosity and restore the elastoviscous properties of synovial fluid, relieve joint pain, and reduce structural damage in the OA joint.

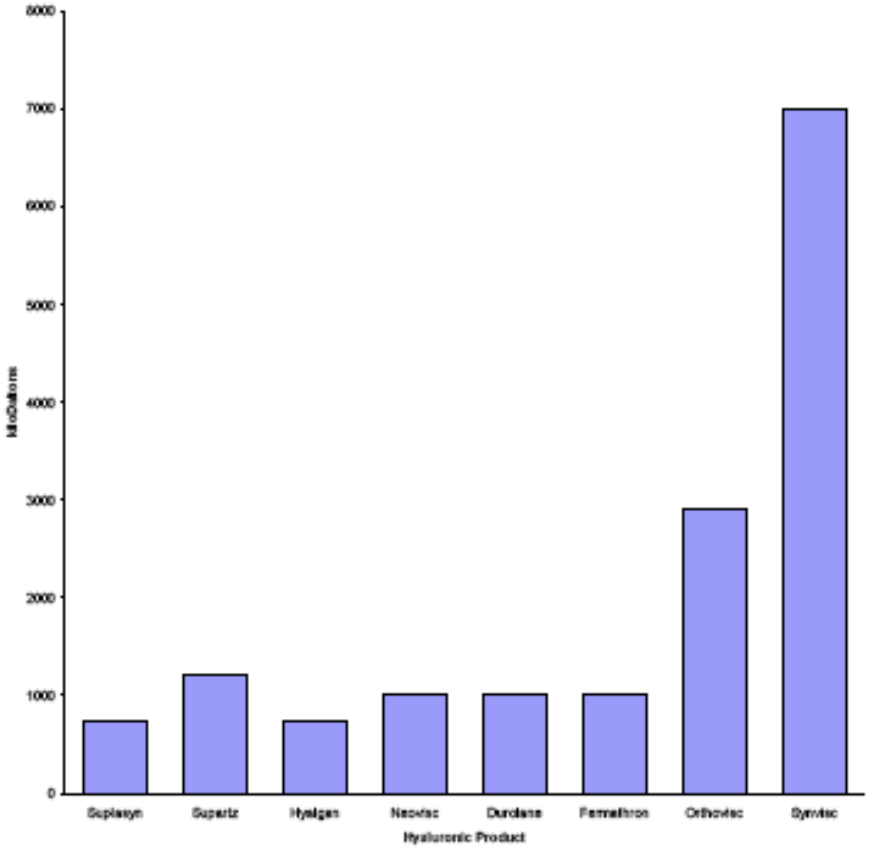
A complete treatment cycle of hylan G-F 20 involves an intra-articular injection of 2 ml of hylan G-F 20 once a week for 3 weeks. This process is called viscosupplementation. It is licensed for use for patients in all stages of joint pathology, but it should not be used in patients who have infected or severely inflamed joints, joints with large effusion, skin diseases or infections in the area of the injection site, or in patients with venous stasis. It is derived from rooster comb hyaluronan; therefore, it is not for patients with hypersensitivities to avian proteins.

Regulatory Status

Health Canada has licensed several products in this class (Appendix 2). The products differ in molecular weight, concentration, volumes utilized, and treatment regimens.

The focus of this review, hylan G-F 20 (brand name Synvisc) is a Class 4 device (licence 8394) manufactured by Genzyme Biosurgery, a division of Genzyme Corporation (Cambridge, MA, United States). It is distinguished from the other products by its chemical structure (i.e., it is a cross-linked hyaluronan, hence hylan) and relatively higher molecular weight, (25) which might bestow greater viscoelastic properties and be more effective than lower molecular weight hyaluronans. (See Figure 2.)

Figure 2: Molecular Weights of Intra-Articular Hyaluronans for Osteoarthritis of the Knee Licensed in Canada



Literature Review on Effectiveness

Objective

The aim if this review was to evaluate the effectiveness of intra-articular hylan G-F 20 for the treatment of pain due to OA of the knee.

Questions Asked

- Does hylan G-F 20 effectively manage pain due to OA of the knee?
- What is the magnitude and duration of the effect of hylan G-F 20 relative to other treatments for pain of OA of the knee?
- What is the magnitude of the effect of hylan G-F 20 as an adjunct to conventional therapy for the treatment of

pain of OA of the knee?
- What is the rate and severity of adverse effects related to intra-articular hylan G-F 20?

Methods

The Medical Advisory Secretariat systematically reviewed the literature to identify evidence on the effectiveness of intra-articular hylan G-F 20 compared with placebo, an alternate treatment, or conventional care according.

Inclusion Criteria

- English-language journal article
- Published between 1966 and February 2005
- Any key trials or reviews published after February 2005 and brought to the attention of the clinical epidemiologist were also included
- Clearly described design and methods
- Study design one of the following:
  - Health technology assessment by recognized institution
  - Systematic reviews or meta-analyses of RCTs on intra-articular hylan G-F 20
  - RCTs of any sample size
  - Non-RCTs comparing intra-articular hylan G-F 20 with an alternate treatment conventional care, or with pre/post comparisons to measure improvement from baseline
- Intervention under study was intra-articular hylan G-F 20 for OA of the knee
- Primary or secondary outcome measure was the level of pain after treatment

Exclusion criteria

- Duplicate publications or studies superseded by a publication with the same purpose, by the same group that included data and outcomes from the same study
- In-vitro studies and animal studies, editorials, letters, and non-systematic reviews
- Reports not available in English
- Unpublished studies
- Abstracts

Databases and search strategy

- Search date: February 1, 2005
- Database searched: Ovid MEDLINE, EMBASE, MEDLINE In-Process & Non-Indexed Citations, Cochrane Database of Systematic Reviews, CENTRAL, and the International Network of Agencies for Health Technology Assessment (INAHTA)
- Search terms: hyaluronan, hyaluronate adj sodium, hylan, hylan G-F 20 (Synvisc), Synvisc, Hyalgan, Orthovisc, Supartz, Artz, Artzal, BioHY, NASHS, NRD101, viscosupplementation, OA, knee, knee joint (See Appendix 3)

One clinical epidemiologist reviewed the abstracts of all of the articles identified through the database search and decided upon eligibility of the study based on the criteria above. When eligibility was not clear based on the information in the abstract, the full text article was retrieved and read.

Extraction of data and assessment of quality

One clinical epidemiologist reviewed the full-text reports and extracted data using an extraction form. Key variables included the characteristics of the patients; method of randomization; type of control intervention; outcome measure for effectiveness, safety, and instrument; and length of follow-up. The Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante in Quebec was reviewing viscosupplementation at the same time the Medical Advisory Secretariat was doing this review. Consequently, one of the AETMIS researchers reviewed the data extracted in this review and assured its accuracy.

The quality of the studies was scored (0–5) using the Jadad scale (26) (Appendix 4), which assigns points for randomization, double blinding, and description of withdrawals and dropouts, as well as additional points for the quality and appropriateness of the randomization and blinding techniques. A score of 5 means the study met all these criteria, whereas a score of 0 means a trial was not randomized, blinded, or analyzed with an intention-to-treat approach. Allocation concealment was evaluated with a letter score:

- A: adequate concealment (e.g., central randomization, serially numbered, sealed envelopes)
- B: unclear (not described)
- C: inadequate concealment (alternation of record numbers)

Studies with randomization that is inadequately concealed can result in selection bias; studies that are not appropriately blinded can result in detection bias. Studies with these shortcomings tend to report effect sizes that are biased toward the intervention. (27;28)

In addition to the Jadad score, the reviewer evaluated the quality of the studies subjectively, by an iterative process of documenting aspects of the study design not captured by the Jadad score, such as the inclusion/exclusion criteria, characteristics of the study populations, validity, and reliability of outcome measures, and any other remarkable aspects of methodological quality.

The GRADE (29) approach (Appendix 4) was used to summarize the overall quality of the evidence. Quality depends on the level of certainty about the magnitude of effect and is based on study design, study quality, consistency of results, and applicability (i.e., directness) to the Ontario clinical context. The GRADE approach also permits one to comment on the strength of recommendations resulting from the evidence, based on estimates of the magnitude of effect relative to the magnitude of risk and burden and the level of certainty around these estimates.

Results of Literature Review

The literature search (Table 4) returned 2 previous health technology assessments, 4 meta-analyses of placebo-controlled trials including a very recent Cochrane review encompassing 18 RCTs that compared hylan G-F 20 compared to either placebo or active treatments, 11 RCTs of hylan G-F 20 (all included in the Cochrane review), and 10 observational studies (2 comparison studies and 8 case series). The difference between the number of RCTs identified in the Cochrane review and those identified in the Medical Advisory Secretariat's literature search can be attributed to non-English (1), unpublished (2), not identified in databases, (3) and different outcome (1). Given the preponderance of evidence, the Medical Advisory Secretariat analysis focused on the Level 1 evidence (i.e., the meta-analyses and RCTs). In this review, the results of the health technology assessments are presented separately from meta-analyses, owing to the differences between their authors, methods, and aims. (30)

Table 4: Quality of Evidence of Studies

Study Design	Level of Evidence	Number of Eligible Studies
Meta-analysis of RCTs*	1a	4
Large RCT	1	3
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT‡	2	8
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	2
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	4
Case series (single site)	4c	4
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

*RCT refers to randomized controlled trial.
†g indicates grey literature.
‡Non-English language and unpublished RCTs not included.

Summary of Existing Health Technology Assessments

In 2003, the Medical Services Advisory Committee (MSAC) (31) in Australia assessed intra-articular viscosupplementation for as a treatment for OA of the knee. Placebo-controlled trials were excluded, because they usually involved saline administration, which is "not part of the clinical pathway for the treatment of knee OA and so was not considered a legitimate comparator." The comparators included NSAIDs, intra-articular steroids, other hyaluronans, and conventional care. Subset analyses were conducted on trials that looked at hylan G-F 20 as the intervention to assess its effectiveness in comparison with the lower molecular weight hyaluronans. The MSAC found 10 RCTs, 4 of which (32-35) looked specifically at hylan G-F 20.

The MSAC concluded that the evidence is sparse (Table 5). Hylan G-F 20 G-F was associated with some improvement at 26 weeks, but by itself was no more effective than NSAIDs or intra-articular steroids. There was evidence that combing hylan G-F 20 with appropriate care produced significant improvements in pain, but the MSAC noted also that this evidence should be interpreted cautiously, owing to a possible bias in the study design. According to the MSAC, the study in question (Raynauld 2002)(36) was completely unblinded, which suggests there were issues with reporting bias.

Further, "the promise of compensation of a free course of the hylan G-F 20 at the completion of the trial for patients in both control and experimental groups insinuates that the product is superior from the outset." Evidence that hylan G-F 20 is more effective than lower molecular weight hyaluronans was inconclusive due to poor reporting. When compared with alternate treatments, intra-articular hyaluronans were the most expensive. They cost 60% more than nonselective NSAIDs and 30% more than COX-2 inhibitors. Based on the evidence, the MSAC recommended that public funding should not support intra-articular viscosupplementation to treat OA of the knee.

Table 5: Overview of Health Technology Assessments

Study, Year	Search Limit	Number of Studies	Control Group Treatments*	Results: Primary Outcome Change in Pain
CAHTA, 2003 (37)	1966–1999	14 studies: 7 RCTs* All hylan	Placebo: 4 NSAID: 1 IA HA: 1 Other: 1	- Small, clinical benefit over placebo up to 3–6 months. - Comparable efficacy to NSAIDs. - Hylan G-F 20 more effective than low molecular weight HA - Repeat course similar to baseline course - Local adverse reaction 0%–2.7% injections. - No systemic adverse reactions
MSAC, 2003 (31)	1966–2002 (August)	10 studies: 4 hylan 6 IA HA	Hylan NSAID: 2 IA Steroid: 1 Other: 1 IA HA NSAID: 2 Steroid: 2	- Evidence on safety is cursory - Local adverse event range 3%–18% - IA HA no more effective than NSAID or IA steroids - Hylan G-F 20 alone no more effective than NSAID, may be synergistic with NSAID - Comparison between hylan G-F 20 and other IA HAs is inconclusive due to poor evidence

*IA indicates intra-articular; IA HA, intra-articular hyaluronan; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial.

In 2003 the Catalan Agency for Health Technology Assessment (CAHTA) (37) systematically reviewed the evidence on the effectiveness of hylan G-F 20. Searching publications between 1966 and 1999, they identified 7 RCTs (38);Scale, 1994 309 /id;Wobig, 1998 89 /id;Raynauld, 2002 44 /id;Wobig, 1999 274 /id;Dickson, 2001 255 /id;Adams, 1995 105 /id} and 7 non-RCTs. Based on their review, they concluded that "there was good evidence that hylan G-F 20 is safe, provides a short-term decrease in pain, and improves function, although the clinical significance of the magnitude of the decrease in pain was likely small". The authors suggested that hylan G-F 20 may be preferable to NSAIDs in patients who cannot tolerate NSAIDs, although no studies included in their review looked specifically at this question or population. They concluded that claims that intra-articular hyaluronan delays the need to have knee surgery are based on only level 4 evidence, and there was insufficient evidence to draw conclusions about the effect of multiple treatments.

Three of the 4 RCTs included in the MSAC review were also included in the CAHTA review. Combined, the results of the 2 health technology policy assessments appear to reach the same conclusions: that intra-articular hyaluronans are effective in the short term, but that the clinical significance of the magnitude and duration of decrease in pain is small. Intra-articular hyaluronans appear to be no more effective than available alternatives (NSAIDs and intra-articular steroids). The 2 assessments reached different conclusions about the safety of intra-articular hyaluronans and about the relative effectiveness of hylan G-F 20 compared to lower molecular weight hyaluronans.

Meta-Analyses

Since the 2 above-mentioned assessments were published in 2003, 4 meta-analyses on the effectiveness hyaluronans have been conducted (Table 6). Two of these are recent publications (published in the month prior to completion of this review). Their results and impacts have yet to be digested and appraised fully by the scientific community. Three of the reviews [Wang, (39) Lo, (40) and Arrich (41)] were similar in that their analyses included only placebo-controlled randomized trials that looked at a hyaluronan as treatment interventions and reported outcomes in a quantifiable measure that can be summarized.

However, the summary outcome measures of these meta-analyses differed. The fourth review, a Cochrane review by Bellamy and colleagues, (24) included all RCTs in which any hyaluronic viscosupplement was administered either in a treatment or a control arm, and analyzed the effectiveness of individual hyaluronans against the available range of control treatments (placebo, NSAIDs, intra-articular steroids, other hyaluronic products, conventional care, and other treatments). Because the scope and potential impact of the Cochrane review conducted by Bellamy et al. is large, it is described in detail and discussed separately.

Table 6: Meta-Analyses of Randomized Controlled Trials of Hylan G-F 20 and Other Hyaluronans

Study, Year	Number of Trials	Primary Outcome Measure	Results on Effectiveness	Results on Safety
Lo, 2003 (40)	Total: 22 Hylan: 3 Scale (1994) (42) Wobig (1998) (43) Karlsson (2002) (44)	Standardized mean difference between treatment and controls of change from baseline pain at 2 months	Pooled effect size for hyaluronic acid was small: 0.32 (95% CI 0.17–0.47). Relative effectiveness of hylan G-F 20 inconclusive	Not mentioned
Wang, 2004 (39)	Total: 20 Hylan: 3 Scale (1994) (42) Dickson (1998)(34) Wobig (1998)(43)	Pooled sum of pain intensity differences (SPID%)* Pooled relative risk of minor adverse events	SPID = 7.9% (95% CI 4.1%–11.7%) Intra-articular hyaluronans are efficacious. Uncertain about the relative effects of different types of hyaluronic products.	- Pooled relative risk of minor adverse events 1.19 - Major adverse event rate 3/1002 (0.2%) - Major adverse event rate among hylan G-F 20 treated 1/139 (0.7%)
Arrich, 2005 (41)	Total: 22 Hylan: 3 Scale (1994)(42) Wobig (1998)(43) Karlsson (2002)(44)	Mean difference on a 100 mm VAS scale of pain with movement	Mean difference on 100 mm VAS at 10–14 and 22–30 weeks was not clinically significant -4.3 (95% CI, -7.6, -0.9) -7.1 (95% CI, -11.8, -2.4) No evident relationship between effect size and molecular mass of HA	Relative risk of adverse events 1.08 (95% CI, 1.01–1.15)
Bellamy, 2005 (24)	Total: 63 Hylan: 17 (see following section)	Unadjusted post-test scores for pain, function, global assessment using weighted mean difference, standardized mean, absolute change from baseline and % change from baseline	Hylan: Superior to placebo; superior to steroids at 5–13 and 14–26 weeks, and comparable to NSAIDs; superior to appropriate care IA HA as a class: Viscosupplementation is effective on pain,	Hylan: No statistically significant adverse event rate IA HA as a class: No major safety issues

Study, Year	Number of Trials	Primary Outcome Measure	Results on Effectiveness	Results on Safety
			functioning, and global assessment, esp. at 5–13 weeks The clinical effects of different products varied.	

*SPID% calculated as follows: sum of pain intensity differences (outcome-baseline) x 100% (maximum scale of pain intensity x trial duration)

The first 3 meta-analyses were based on 20 to 22 RCTs that compared the efficacy of a hyaluronan with a placebo. In each analysis, only 3 of the studies specifically looked at hylan G-F 20 as the intervention treatment. The Arrich meta-analysis (41) did not include any efficacy or safety outcome data from Scale, only used safety outcome data from Wobig and safety and WOMAC function outcomes from Karlsson, but no pain outcomes.

Each meta-analysis used different summary measures. The Lo study, (40) which derived a pooled effect size of 0.32 (0.17–0.47), and the Arrich study, which reported a mean difference on a 100 mm visual analogue scale for pain of -6.0 (-22.3–10.3), each concluded that intra-articular hyaluronan has a small-to-negligible effect on pain. The Wang (39) meta-analysis, which calculated and reported pooled mean differences in efficacy scores in the range of 7% to 13%, came to the different conclusion that hyaluronan leads to significant improvements in pain and functional outcomes. However, Arrich et al. criticized the summary measure Wang used, saying it made drawing clinical inferences difficult.

With respect to the effect size of hylan G-F 20 compared with the lower molecular weight hyaluronans, the evidence is inconsistent. Both the Wang and Lo papers observed that the trials involving hylan G-F 20 had bigger pooled estimates of effect than did the trials of the lower molecular weight hyaluronan, although heterogeneity among the hylan G-F 20 studies prevented the drawing of definitive conclusions. The Arrich paper, on the other hand, conducted a meta-regression analysis according to molecular mass and concluded that no clear association between molecular weight and effect size was evident. However, this conclusion was drawn on only a small number (3) of studies that looked specifically at hylan G-F 20, and drawing such a conclusion may be over-interpreting the strength of the data.

Only 2 (39;41) of the meta-analyses reported data on safety. Both identified a slightly increased risk of minor adverse events among patients who received hyaluronan rather than placebo. According to the Wang study, the rate of serious adverse events related to hylan G-F 20 administration, defined as a painful acute local reaction, was 0.7%.

Overall, it is difficult to draw strong conclusions about the safety and efficacy of hylan G-F 20 from these meta-analyses, because they included only a small number of trials and used different summary outcome measures.

The Cochrane Review

The Bellamy (24) review was released in 2005 and aimed to identify all RCTS of intra-articular hyaluronic products used to treat OA of the knee. Control treatments included placebo, defined as saline or arthrocentesis, and active treatment. The primary outcome measures, consistent with OMERACT III criteria, were unadjusted post-test scores of any of pain, physical function, patient global assessment, and

joint imaging. The authors tested for heterogeneity presented summary measures using the calculations suggested by the Cochrane Handbook, in terms of WMD, standardized mean difference when scales were inconsistent, absolute reduction from baseline, and percentage reduction from baseline. The quality of the studies was rated using the Jadad score. The results are presented by products and for the whole class of viscosupplements at 4 predetermined end points after treatment: 1 to 4 weeks, 5 to 13 weeks, 14 to 26 weeks, and 45 to 52 weeks.

Results: 63 trials with a median Jadad score of 3 were identified. Thirty-seven trials compared hyaluronan or hylan G-F 20 with placebo, 9 trials compared a viscosupplement with intra-articular corticosteroids, and 5 trials compared a hyaluronic product with NSAIDs. The authors concluded that the pooled analyses supported the efficacy of this class of hyaluronic products. In the 5-to-13 week postinjection period, there was an improvement from baseline of 11% to 54% for pain and 9% to 15% for function. In general, comparable efficacy was noted against NSAIDs, and longer-term benefits were noted compared with corticosteroids. Few adverse events were reported. Differential efficacy effects were observed for different products on different variables at different time points.

Seventeen of the studies, comprising 23 separate comparisons included in the Cochrane Review, involved hylan G-F 20. The Medical Advisory Secretariat undertook a subanalysis of these 17 studies.

Medical Advisory Secretariat Subanalysis

The objective of the Medical Advisory Secretariat subanalysis was to do impose more rigorous criteria on the interpretation of the results of these 17 studies by:

- Distinguishing clinically significant results from statistically significant results by identifying studies that report a difference in outcome pain scores among subjects treated with hylan G-F 20 compared with patients in the control group that clearly exceed the minimal clinically significant thresholds outlined in Table 2, and
- Distinguishing high-quality studies from low-quality studies and drawing conclusions and basing recommendations primarily on the results of high-quality studies.

The 17 studies that involved hylan G-F 20 are described in Appendix 5. Some of these were unpublished or were not English-language studies; therefore, the Medical Advisory Secretariat could not interpret or appraise them, particularly with respect to their quality. Consequently, the bulk of this subanalysis is based on the published studies that the Medical Advisory Secretariat could access (i.e., those that were English-language studies). Overall, the 17 studies had a mean Jadad score of 2.9. They varied in their length of follow-up periods; in their length to outcome; type of outcome measure and instrument used; and extent of concomitant therapy permitted. Comparators were placebos, intra-articular steroids, NSAIDs, other intra-articular hyaluronans, and appropriate care without hylan G-F 20.

Evidence of clinical effectiveness of Hylan G-F 20 (Medical Advisory Secretariat's Subanalysis)

Trials of Hylan G-F 20 Versus Placebo

Table 7: Placebo-Controlled Trials

Study, Year	Sample Size	Quality (Jadad Score/5)
Ardic, 2001* (45)	17	1
Dickson, 2001 (34)	165 (3 arms)	4
Groppa, 2001* (46)	25	1
Karlsson, 2002 (44)	246 (3 arms)	5
Moreland, 1993* (38)	94	5
Scale, 1994a (2 inj) (42)	50	4
Scale, 1994b (3 inj) (42)	30	4
Wobig, 1998 (43)	110	4
Wobig, 1999c* (NEhyl) (47)	132 (4 arms)	4

*Original study not reviewed by the Medical Advisory Secretariat.

Of the 9 trials that compared hylan G-F 20 with placebos, 6 reported a difference in the VAS score for pain with weight bearing at 1 to 4 weeks after treatment. The 3 trials that did not report an outcome at this endpoint were Ardic, (45) Groppa, (46) and Dickson (34). The 6 remaining studies that reported the outcome were sufficiently homogenous (I^2, -64.8%) to be combined, producing a weighted mean estimate (and 95% CI) of -12.54 (-20.4 to -4.7) that failed to exceed with confidence the MCID threshold of 10 mm imposed by the Medical Advisory Secretariat. Five trials reported this outcome at 5 to 13 weeks after treatment. The level of heterogeneity among the studies (I^2, 82.9% was deemed excessive according to Medical Advisory Secretariat criteria. Three of the 5 studies reported outcome pain levels that clearly exceeded the MCID. Two of these (scale a and scale b) were 2 arms of a very small trial. At 14 to 26 weeks, 4 studies reported outcomes at this level. Two reported a treatment effect that clearly exceeded the MCID threshold; 2 did not. Overall evidence of a clinically significant difference in pain reduction between the treatment and control groups was inconsistent.

Trials of Hylan G-F 20 Versus Intra-Articular Corticosteroids

Table 8: Trials Comparing Hylan G-F 20 With Intra-Articular Corticosteroids

Study, Year	Sample size	Quality (Jadad Score/5)
Leopold, 2003 (48)	100	3
Caborn, 2004 (49)	218	2

The trial by Leopold et al. (48) found a modest improvement in pain in both the hylan G-F 20 and intra-articular steroid arms, but the differences between the arms were not significant. The Caborn (49) trial reported outcomes using a 0 to 4 Likert scale rather than 100 mm VAS scores. The Caborn trial reported a statistically significant difference in favor of hylan G-F 20 compared with triamcinolone hexacetonide for WOMAC pain walking on a flat surface (scored 0 to 4) at 5 to 13 weeks post-injection (WMD, -0.40; 95% CI -0.65 to -0.15) and at 14 to 26 weeks (WMD, -0.40; 95% CI-.0.68 to -0.12) post-injection. However according to Medical Advisory Secretariat criteria, the CI failed to exceed clearly the MCID threshold of 0.4 (Table 2). The authors reported that hylan G-F 20 was 17% more effective than triamcinolone hexacetonide. Again, according to Medical Advisory Secretariat criteria, the size of the effect did not reach the MCID threshold of 20%.

Trials of Hylan G-F 20 Versus Nonsteroidal Anti-Inflammatory Drugs

Table 9: Trials Comparing Hylan G-F 20 With Nonsteroidal Anti-Inflammatory Drugs

Study	Sample size	Quality (Jadad Score/5)
Adams (1995) (35)	102	3
Dickson (2001) (34)	165 (3 arms)	4

Adams (35) found no statistically significant differences in any of the efficacy outcome measures. There was a statistically significant difference in favour of hylan G-F 20 compared with NSAIDs in the WOMAC subscale (0 to 100 mm VAS) (WMD, -12.00; 95% CI, -23.09 to -0.91) at 5 to 13 weeks post-injection in the Dickson (34) study; however, according to Medical Advisory Secretariat criteria, the 95% CI surrounding this estimate failed to exceed clearly the MCID threshold. In terms of safety, there was a statistically significant difference in favour of hylan G-F 20 compared with NSAIDs for the number of patients with possible or probable related systemic adverse events at 5 to 13 weeks post-injection (RR, 0.46; 95% CI, 0.25–0.83; $P = .01$). The number need to treat was 4.

Trials of Hylan G-F 20 Versus Other Hyaluronans

Table 10: Trials Comparing Hylan G-F 20 With Other Hyaluronans

Study, Year	Sample size	Quality (Jadad Score/5)
Karlsson, 2002 (44)	246 (3 arms)	5
Wobig, 1999b (47)	132 (4 arms)	4
Wobig, 1999a (47)	132 (4 arms)	4
Bayramoglu, 2003 (50)	46	2
Brown, 2003 * (51)	54	1
Thompson, 2002 * (52)	321	2

*Original study not reviewed by the Medical Advisory Secretariat.

According to Figure 201 in the review by Bellamy, (1) there was sufficient homogeneity among the 3 higher-quality studies to generate a summary estimate of the WMD in outcome pain scores at 1 to 4 (-2.06; 95% CI, -7.45 to 3.32) and 5 to 13 weeks (-6.59; 95% CI, -12.46 to -0.73) after injection. However, the WMD failed to exceed clearly the MCID threshold of -10 defined by the Medical Advisory Secretariat at these end points. Only 1 study (44) presented outcomes at 14 to 26 weeks after injection. The mean difference (-5.00; 95% CI, -14.98 to 4.98) was not clinically significant according to Medical Advisory Secretariat criteria.

Trials of Hylan G-F 20 Versus Appropriate Care

Table 11: Trials Comparing Hylan G-F 20 With Appropriate Care

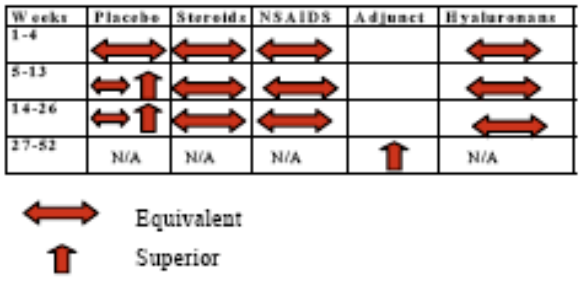
Study, Year	Sample size	Quality (Jadad Score/5)
Raynauld, 2002 (32)	255	3
Kahan, 2003 (53)	518	3

The Raynauld (32) and Kahan (53) studies were open-label studies that compared hylan G-F 20 plus conventional care, defined as any appropriate nonpharmacological, pharmacological, complementary, or surgical intervention, with only conventional care The studies measured the primary outcome (pain with movement) with different scales. Raynauld found a statistically significant between-group difference that favoured hylan G-F 20 plus appropriate care at 45 to 52 weeks after injection as measured by the WOMAC pain subscale (0–20 Likert) (WMD, -3.16; 95% CI, -4.17 to -2.15). Assuming that the validity of this Likert scale can be maintained by dividing it by a factor of 5 to place it on the more conventional 4-point scale, the lower bound of the CI (-2.14/5 = - 0.43) exceeds the MCID according to Medical

Advisory Secretariat criteria (Table 2). Similarly, Kahan found a statistically significant between-group difference in favour of hylan G-F 20 and appropriate care as measured by the WOMAC OA Index pain subscale (0–100 mm VAS) (WMD, -12.7; 95% CI, -16.4 to -8.9). Patients that received hylan G-F 20 plus appropriate care experienced a 21.5% to 25% reduction in pain compared with baseline, which just exceeds the MCID threshold (Table 2). In terms of safety, there was no statistically significant difference in the number of patients reporting side effects from baseline (RR, 0.94; 95% CI, 0.44–2.02). Significantly more patients in the appropriate care only group reported adverse effects compared with those in the combination group (68% vs. 52%).

A summary of the Medical Advisory Secretariat subanalysis of the clinical significance of the results reported in the 18 RCTs of hylan G-F 20 compared with placebo and active treatment is shown in Figure 3. According to the Medical Advisory Secretariat's analysis, there is some evidence that hylan G-F 20 is clinically better than placebo at 5 to 13 weeks after treatment; however, the evidence that hylan G-F 20 is clinically better than placebo at 14 to 26 weeks is inconsistent. There is also evidence that adding hylan G-F 20 to conventional care is clinically better than conventional care only at 36 to 52 weeks after injection, and that hylan G-F 20, is equivalent, but not clinically superior, to NSAIDs, intra-articular corticosteroids, and other hyaluronans on magnitude of pain relief at 1 to 26 weeks after treatment.

Figure 3: Summary of Medical Advisory Subanalysis of Clinical Significance of Results



Quality of Studies of Hylan G-F 20 (Medical Advisory Secretariat Subanalysis of Cochrane Review)

The Cochrane review by Bellamy et al. (24) on viscosupplementation for OA of the knee was released just as the Medical Advisory Secretariat finished its literature search and data extraction for its review. Consequently, the Secretariat's familiarity with most of the studies in the Cochrane review permitted it to evaluate the quality of the individual studies. According to a recent meta-analysis, (54) many systematic reviews, including Cochrane reviews, fail to take into account the quality of the studies when they interpret the results.

To assess the quality of the evidence, the Medical Advisory Secretariat adopted the GRADE approach,

(29) which considers the study's design and quality, and the consistency of estimates of effect and applicability (i.e., directness) of people, interventions, and outcome measures. (See Appendix 4.) This exercise enabled the Secretariat to identify the high-quality studies, assess the overall quality of the evidence available through the Cochrane review, and modulate recommendations on the clinical utility of hylan G- F 20.

GRADE criteria:

Study design

Initially, this literature review (Table 4) identified and considered including 10 observational studies, 2 of which assessed the safety and effectiveness of repeat treatments of hylan G-F 20, and 8 that looked at its safety and effectiveness. In the end, however, only the safety outcomes from these studies were included, because there were RCTs to measure effectiveness, and because of the compromised quality of these observational studies (summarized in Appendix 6).

Study Quality

The limitations of the methods that were identified in some of the RCTs on hylan G-F 20 are described in Table 12. The impact of a limitation on study quality is a matter of judgment. For this review, the following criteria were used to identify significant limitations: The Jadad score indicates that appropriate randomization, blinding, and accounting for drop-outs are key quality measures of RCTs. Consequently, any RCT with a Jadad score lower than 3 was deemed to have significant limitations. In addition, failure to blind, despite a Jadad score of 3, was considered a significant limitation because of the potential for detection bias. Offering the incentive of free treatment of hylan G-F 20 upon completion of the trial was also considered a serious limitation, because it implies that treatment with hylan G-F 20 is superior.

Other limitations pertained to treatments that were not equivalent between arms (in particular, whether arthrocentesis was performed on both intervention and control groups), subtherapeutic dosing in control groups, and significant differences in influential baseline characteristics between treatment and control groups, which implies a problem with randomization.

Table 12: Concerns With the Quality of the Evidence of the Randomized Controlled Trials of Hylan G-F 20*

Trial Reference Number†	Study	Jadad Score	Description of Significant Limitations
1 2	Adams(35) A – NSAID B – NSAID + hylan	3	- Possible contamination of treatment arm after 12 weeks. - Hylan G-F 20 group may not have been blinded, because they were told to stop NSAIDs. - There appears to have been no washout period prior to baseline measurement.
3	Ardic (45)	1	- Low Jadad score.
4	Auerbach (55)	2	- Low Jaded score (German-based study).
5	Bayramoglu (50)	2	- Low Jadad score. - Outcome instrument (Index Severity of Knee) did not provide a discrete pain measure.
6	Brown (51)	1	- Low Jadad (and trial discontinued).
7	Caborn (49)	2	- Low Jadad score. - Single-blinded (patients not blinded). - Control treatment of an injection of steroids over 6 months may be subtherapeutic; guidelines recommend one every 4 months.

Trial Reference Number†	Study	Jadad Score	Description of Significant Limitations
8 9	Dickson (34) Steroid Placebo	4	No apparent significant limitations.
10	Groppa (46)	1	Low Jadad score.
11	Kahan (53)	3	Open label and use of concomitant medications not reported.
12 13	Karlsson(44) Placebo B-HA	5	No apparent significant limitations.
14	Leopold (48)	3	- Effusions of steroid-control group were not aspirated and could have reduced effectiveness of steroid treatment, although authors were following instructions on package insert for corticosteroids.
15	Moreland (38)	5	- Incentive to complete phase 1 (10 weeks) and enter phase 2, in which all participants received at least one course of hylan G-F 20. - Consequently possible detection bias - Published abstract only.
16	Raynauld (32)	3	- Open-label study.
17 18	Scale (42) (2 injections) (3 injections)	4	- Treatment subtherapeutic. - Quality of reported study very poor. - Text and figures give different information. - Difficult to extract measures of standard deviation and confidence intervals.
19	Thompson (52)	2	- Low Jadad score. - German language study. - Published abstract.
20	Wobig (1998) (43)	4	- No apparent significant limitations
21 22 23	Wobig (47) A - (Artz) B - (Healon) C - (Nonelastoviscous hylan)	4	- Only Artz comparison published. - Not published. - Not published.

*As appraised by the Medical Advisory Secretariat.
†See Table 14.

Consistency

The consistency of the estimate of effect depends in part on the magnitude of effect deemed significant. When a magnitude of effect is deemed significant (i.e., if the mean difference in outcome pain scores between the treatment and control group exceeds zero), then, based on the Cochrane review by Bellamy, there's evidence that hylan G-F 20 is superior to placebo at 4 to 26 weeks after injection, to intra-articular corticosteroids at 4 weeks after injection, to other hyaluronans, to conventional treatment without it, and that it is equivalent to NSAIDs.

However, when a threshold difference of at least 10 mm on a 100 mm VAS scale is deemed the MCID, then, as the Medical Advisory Secretariat's analysis suggests, there is evidence that hylan G-F 20 is equivalent to NSAIDs, intra-articular steroids, other hyaluronans, and placebo at 4 weeks after injection. There is also evidence that hylan G-F 20 is better than conventional care without hylan at 36 to 52 weeks after treatment, and, finally, the evidence that hylan G-F 20 is superior to placebo between 4 and 26

weeks after treatment is inconsistent.

Directness

Directness refers to the extent to which the people, interventions, and outcome measures are similar to those of interest. To some extent, the directness of the outcome measures has been discussed in the point on consistency, because one's interpretation depends on the magnitude of effect of interest. From the perspective of the Medical Advisory Secretariat, a clinically significant difference in pain is more relevant than a statistically significant difference. In terms of the characteristics of the participants, in nearly every RCT on hylan G-F 20, the inclusion criteria included individuals with OA of the knee with persistent moderate-to-severe pain (i.e., baseline VAS > 40 mm), despite conventional care. No study looked at individuals for whom NSAIDs were contraindicated, and only one looked at the clinical utility of hylan G-F 20 in patients with advanced disease (defined on the basis of pain, disability, radiographic grade, and duration of disease), for whom total knee replacement may be imminently indicated.

However, the greatest area of uncertainty when assessing the directness of the evidence on hylan G-F 20 has to do with the appropriateness of its placement among the options for managing pain due to arthritis, particularly among the placebo-controlled trials. There was a great deal of heterogeneity in the definitions of the studies' intervention treatments. Few isolated hylan G-F 20 as the only intervention. Some permitted break-through analgesics (any of Tylenol, NSAIDs, opiates, to varying degrees and doses), some conducted arthrocentesis, some conducted saline lavage, and some administered hylan G-F 20 as an adjunct to conventional care, which may have included physiotherapy, acupuncture, arthroscopic debridement, and total knee replacement. Consequently, it is difficult to draw conclusions about the clinical indications for which hylan G-F 20 is most appropriate as a substitute versus an adjunct.

Table 13: Summary of GRADE Quality of Evidence of Trials Comparing the Effectiveness of Hylan G-F 20 to Other Treatments for Pain Due to Osteoarthritis of the Knee

Other Treatment (Comparator)	No. of Studies	Design	Quality	Consistency	Directness	Quality of Evidence
Placebo	9	RCT*	Serious limitations	No	No	Very low
Intra-articular steroids	2	RCT	Serious limitations	Yes	Yes	Moderate
NSAIDs*	2	RCT	Serious limitations	Yes	Yes	Moderate
Intra-articular hyaluronans	5	RCT	Serious limitations	Yes	No	Low
Conventional care†	2	RCT	Serious limitations	Yes	Yes	Moderate

*NSAID indicates nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial.
†Conventional indicates appropriate.

Using the GRADE approach, one might conclude that there is moderate evidence that hylan G-F 20 plus conventional care is more effective than conventional care without hylan G-F 20, and that hylan G-F 20 is equivalent to NSAIDs and intra-articular steroids. There is low-quality evidence and, hence, uncertainty about the effectiveness of hylan G-F 20 compared to placebo or other hyaluronan products.

However, in using the GRADE approach, several limitations were identified in the evidence that limit the strength of the conclusions that can be drawn when all RCTs on hylan G-F 20 are considered. Consequently, the Medical Advisory Secretariat undertook to identify the high-quality studies, which meant excluding studies with serious limitations (Table 14). As a result, only 4 high-quality studies

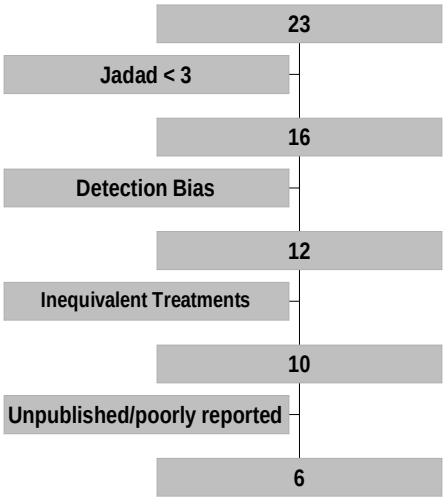
(Table 15, Figure 4) involving 6 comparisons were identified. These are reviewed in some detail.

Table 14: Trials Excluded From the Medical Advisory Secretariat's Review

Reason for exclusion	Studies*
Jadad score less than 3	3, 4, 5, 6, 7, 10, 19
Patient not blinded, or there was an incentive to complete	1, 2, 11, 16, 14
In equivalent treatments, there were significant differences in patient characteristics between arms or subtherapeutic treatments	17, 18,
Unpublished or poorly/sparsely reported studies	22, 23, 15

*Reference number: see Table 12.

Figure 4: Number of and Reasons for Excluded Comparisons*



*Some trials had multiple arms/comparisons.

Table 15: Summary of Higher-Quality Studies

Study	Size	Patients	Weeks 1-4	4-13	14-26
Karlsson	Hylan 86 Placebo 66 Artz 90	Mean Age 71 Baseline VAS 63 Severly disabled Surgery indicated	↔	↔	↔
Wobig 98	Hylan + conventional care 52 Placebo + conventional care 54	Mean Age 62 Baseline VAS 71 Daily persistent pain despite analgesics		↑	↑
Wobig 99	Hylan 38 Artz 32	Mean age 60 Persistent pain despite NSAIDS		↔	N/A
Dickson	Hylan 53 Diclofenac 55 Placebo 57	Mean age 63 VAS 59		↔	N/A

Karlsson (44)

Design: This was a double-blinded, multicentre RCT of 246 patients who were allocated to one of 3 arms (hylan G-F 20, Artzal, or placebo). According to the authors' power calculations, 50 patients were needed in the placebo group, 75 in each of the 2 active treatment groups, to enable detection of a difference of 15 mm in the decrease in weight-bearing pain from baseline between the placebo and active treatment groups. Per-protocol (hylan G-F 20 (N = 77), Artzal (N = 76), placebo (N = 57) and intention-to-treat (hylan G-F 20) (N = 86), Artzal (N = 90), placebo (N = 66)) analyses were conducted. There was a 2-week washout period before measuring baseline scores. Breakthrough acetaminophen up to 4 grams a day was permitted, but not within 12 hours of outcome assessments. The study ran for 1 year. The primary outcome was weight-bearing pain between 0 and 26 weeks after treatment and duration of clinical benefit over 0 to 52 weeks. Clinical failure was defined as the use of concurrent treatment for the study knee.

Patients: Swedish study. Inclusion criteria were age over 59 years, advanced disease (Lequesne score of at least 10), weight-bearing pain of at least 40/100 mm VAS, radiological confirmed OA grade I or II by Ahlback criteria, and a normal physical exam. The exclusion criterion was any intra-articular procedure in the study knee within the previous 6 months. The mean age of the subjects was 71 years. Baseline values were nearly equivalent among the 3 arms: 100 mm VAS weight-bearing pain, 63 to 65; total WOMAC score, 48.7 to 48.9; total Lequesne score, 13.4 to 13.9.

Results: Patients in all 3 arms improved significantly from baseline. However, the magnitude of difference between the hylan G-F 20 and placebo arms at 5 to 13 weeks after treatment (WMD, -5.0; 95% CI, -18.6–8.65), and at 14 to 26 weeks after treatment (WMD, -1.0, 95% CI; -14.5–12.6), was not clinically significant. Nor was it clinically significant between the hylan G-F 20 and Artz arms at 5 to 13 weeks (WMD, -1.0; 95% CI, -9.8–7.8) or at 14 to 26 weeks (WMD, -5.0; 95% CI, -15.9–4.9) after treatment. Compared with placebo, neither of the hyaluronic acid treatments had a significantly longer duration of clinical benefit. By week 26, 20% to 30% of participants had dropped out. By week 52, this had risen to 60% to 70%.

Wobig 1998 (43)

Design: This was a double-blinded, multicentre RCT of 110 patients randomized to receive either hylan G-F 20 (N = 52) or placebo (N = 54).The authors did an intention-to treat analysis. There was a 2-week washout period prior baseline measures were taken Concurrent therapy was permitted throughout the trial, which included steroids, NSAIDs, analgesics, physiotherapy, and surgery. One of the primary outcomes was pain with weight bearing. The study lasted 12 weeks, and there was a follow-up phone call at 26 weeks.

Patients: German study. Although anyone older than 18 was permitted to enter, the mean age was 62 years. Inclusion criteria were radiological evidence and persistent pain despite use of NSAIDs or analgesics. The mean duration of disease was 6 years. The baseline 100 mm VAS scores for pain with weight bearing were virtually the same between the treatment and control groups (71 mm and 75 mm, respectively). There was some imbalance between the treatment and control groups: significantly more patients in the hylan G-F 20 group had had the disease for less than 1 year, and their disease was less advanced according to radiographic (Larsen) grades. However, an analysis of variance, breaking the study sample down by population and Larsen grade, showed no significant treatment-by-grade interactions.

Results: More patients in the hylan G-F 20 group reported clinically significant improvements in outcome VAS pain scores compared with the placebo group at 5 to 13 weeks after treatment (WMD, -37.0; 95% CI, -45.3 to -28.7) and at 14 to 26 weeks after treatment (WMD, -21.0; 95% CI, -32.1 to -9.9). Rescue therapy was required by only 11% of patients in the hylan G-F 20 group, compared with 53% of

the saline-treated group.

Wobig 1999 (47)

Design: This was double-blinded, multicentre RCT of 70 patients randomized to receive either intra-articular hylan G-F 20 (n = 38) or Artz, another intra-articular hyaluronan (n = 32). There was a 2-week washout of NSAIDs and analgesics. Concurrent therapy was permitted throughout the trial. Primary outcome was weight-bearing pain at 12 weeks.

Patients: German-based study. Although anyone older than 18 could participate, the mean age was 60 years. Inclusion criteria were radiological and laboratory evidence of OA and persistent pain despite use of NSAIDs or analgesics. The mean duration of disease was 4.6 years. The baseline 100 mm VAS scores for pain with weight bearing were virtually the same between the treatment and control groups (70mm and 72mm). Patients with effusions were excluded.

Results: Hylan G-F 20 was significantly more effective at relieving OA knee pain; however, the magnitude of effect on pain with weight bearing at 12 weeks after injection did not exceed the MCID of –10 mm with confidence (WMD, -16.0; 95% CI, -27.1 to -5.0).

Dickson 2001(34)

Design: This was a 12-week, double-blinded, multicentre RCT conducted in 18 general practices in the United Kingdom. It involved 165 patients randomized to one of 3 arms: hylan G-F 20 and placebo pills, arthrocentesis and diclofenac retard 100 mg daily, or arthrocentesis and placebo pills). Up to 3000 mg of break-through paracetamol was permitted.

Patients: British study. Subjects were required to have radiologically confirmed OA and baseline pain exceeding 40 mm on a 100 mm VAS. The baseline WOMAC pain score ranged from 59 to 61, and the baseline Lequesne score ranged from 13.9 to 14.4, indicating the disease was advanced.

Results: The magnitude of effect of hylan G-F 20 compared with diclofenac failed to exceed the MCID of -10 mm with confidence (WMD, -12.0; 95% CI, -23.1 to -0.9). (The per-protocol analysis was underpowered.)

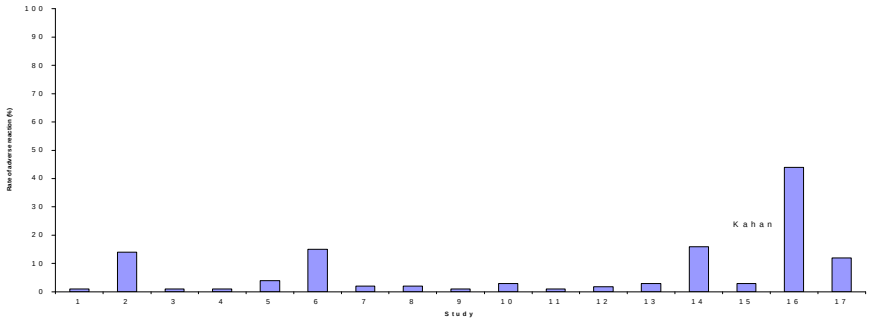
Five of the 6 systematic reviews considered safety. Their conclusions are shown in Table 16.

Table 16: Safety of Hylan G-F 20 According to Level 1a Evidence

CAHTA (37)	There is good quality scientific evidence showing that hylan is safe.
MSAC (31)	Evidence is cursory and conclusions cannot be drawn.
Lo (56)	Not discussed.
Wang (39)	Relative risk of minor, transient injection reaction, 1.19; severe adverse event rate was 3/1002 knees.
Arrich (41)	Small risk of increased adverse events compared to placebo.
Bellamy (24)	Sample-size restriction preclude any definitive comment on the safety of HA class products; however, no major safety issues were detected.

The rates of local adverse events reported in the RCTs and observational studies reviewed by the Medical Advisory Secretariat are shown in Figure 5.

Figure 5: Reported Rates of Local Adverse Reactions With Hylan G-F 20



The 8 Level 4 studies (33;57-63)(Appendix 6), in addition to the RCTs, were reviewed for safety. Twelve of the 17 studies reviewed reported local adverse event rates of less than 5% of either injections or patients. One apparent outlier, Kahan, (53) reported an adverse event rate of 44% among patients in the hylan G-F 20 arm, compared with a 32% rate among the control group. Most (37%) of the hylan-related reactions in this study were due to pain or swelling at the injection site. The results of a retrospective chart review (64) suggested that the risk of a local reaction increased with repeat treatments of hylan G-F 20; however, a recent prospective analysis (65) identified no statistically significant differences in the rates of adverse events between the first and repeat treatment cycles.

The rate of severe adverse reactions to hylan G-F 20 in this review was low, with 5 (4%) moderate to severe events reported in one study, (Clarke (62)) resulting in pain and swelling requiring joint aspiration. There was also one episode of severe arthrosis in another study (Waddell (66)) (1.4%), and 3 (1%) episodes in another (Wobig 1999 (33)).

In 2002, 6 cases of granulomatous inflammation of the synovium after hylan G-F 20 injections were reported. (67) Recently, the Canadian Adverse Reaction Newsletter (68) reported that Health Canada had received 31 reports of suspected incidents associated with hylan G-F 20 between 1996 and 2005; 23 were

received in 2003 to 2004. In 9 cases, synovial fluid was not removed before each injection. Six of the 23 recent reports described patients who had pain, walking disability, and knee swelling, with or without effusion, after the third injection of the first course.

An estimated 5,000 people in Ontario receive hylan G-F 20 treatments a years, which is about 0.04% of the Ontario population. By presuming that a similar proportion of people across Canada receive hylan G-F 20, then an estimated 15,000 people a year are treated with hylan G-F 20. This means that injection with hylan G-F 20 may carry a risk of a moderate-to-severe inflammatory joint reaction; however, the likelihood of this complication appears to be low, at about 23/15,000 (0.15%).

Summary

The 2 health technology assessments found that the data were sparse and poor quality. There was some evidence that hylan G-F 20 delivered a small clinical benefit at 3 to 6 months after treatment on a magnitude comparable to that of NSAIDs and intra-articular steroids. Hylan G-F 20 appeared to carry a risk of a local adverse reaction of 3% to 18% per injection, but no apparent risk of a severe adverse event, although the data were limited.

Each of the 3 meta-analyses of placebo-controlled trials of intra-articular hyaluronans had only 3 trials involving hylan G-F 20. There results were inconsistent, with 1 analysis concluding that intra-articular hyaluronans were efficacious, whereas the 2 others concluded the effect size was small (0.32) and probably not clinically significant. The risk of a minor adverse event ranged from 8% to 19% per injection. Major adverse events were rare.

The Cochrane review concluded that pooled analysis supported the efficacy of hylauronans, including hylan G-F 20. At 5 to 13 weeks after the injection, there was an improvement from baseline of 11% to 54% for pain and 9% to 15% for function. Comparable efficacy was noted against NSAIDs, and longer-term benefits were noted in comparison against steroids. Few adverse events were noted.

When the Medical Advisory Secretariat applied the criterion of clinical significance to the magnitude of pain relief reported in the RCTs on hylan G-F 20 it found the following:

- inconsistent evidence that hylan G-F 20 was clinically superior to placebo at 5 to 26 weeks after treatment,
- consistent evidence that for pain relief, hylan G-F 20 was no better or worse than NSAIDs or intra-articular steroids at 5 to 26 weeks after treatment,
- consistent evidence that hylan G-F 20 was not clinically superior to other hyaluronic products, and
- consistent evidence that hylan G-F 20 delivered a small magnitude of clinical benefit at 12 to 52 weeks after injection when administered as an adjunct to conventional care.

There were substantial limitations to the methods of many of the RCTs involving hylan G-F 20. When only the results from higher-quality studies were considered, there was level 2 evidence that hylan G-F 20 was not clinically superior to placebo (or another hyaluronan) at 1 to 26 weeks after treatment in older patients with advanced disease for whom total knee replacement was indicated. There was level 2 evidence that hylan G-F 2- was comparable to NSAIDs at 4 to 13 weeks after treatment and that it was superior to placebo when delivered as an adjunct to conventional care 4 to 26 weeks after treatment.

Overall, hylan G-F 20 carries a risk of a minor, local adverse event rate of about 8 to 19 per 100 injections. Incidents of moderate-to-sever post-injection inflammatory joint reactions have been reported, but the likelihood appears to be low (0.15% per patient).

Economic Analysis

Literature Review: Objectives and Methods

The objective of the literature review was to identify economic analyses relevant to the Ontario health care system that analyzed the health and economic impact of the use of hylan G-F 20 as a treatment for OA of the knee. The search strategy identified published English-language articles that mentioned the combination of cost, hylan G-F 20, and OA of the knee. The search yielded 24 citations, 3 of which

addressed the economic impact of incorporating hylan G-F 20 (Table 17).

Table 17: Summary of Costing Papers of Hylan G-F 20

Study (Perspective)	Method	Conclusions	Limitations
Waddell (69) (American HMO)	Followed a hypothetical cohort of 3,835 OA* patients for 3 years and estimated the cost-savings that might result from delayed need for TKR* among people eligible for and responsive to hylan G-F 20.	Over 3 years, 808 TKRs were avoided at a cost-savings of $4,706 per OA patient.	- Over-estimated the duration of effect of hylan G-F 20. - There's no evidence that hylan G-F 20 postpones or avoids TKR. - Ignored the downstream costs of TKR for the patients who avoided TKR in the 3-year window.
Kahan (53) (Health System - France)	Compared the total health care costs over 9 months of 518 OA patients randomized to receive either conventional treatment or conventional treatment + hylan G-F 20.	Over 9 months, total mean cost per patient was equivalent. The cost of more visits in hylan G-F 20 group was offset by lower use of certain drugs and hospitalizations	- Cost of Synvisc was estimated at a 65% reimbursement rate to patient. - 9 months is a short window. - Open-label trial. - Costs not generalizable to Ontario.
Torrance (70) (Societal) (Health system)	Randomized 255 patients to receive either appropriate care or appropriate care + hylan G-F 20 and calculated mean OA-related cost.	Mean annual OA-related cost per patient in the hylan group exceeded the control by $710 (95% CI, $147–$1273). 69% of hylan G-F 20 patients vs. 40% in AC group improved† at 12 months. The AC + hylan G-F 20 group gained 0.071 (95% CI, 0.017–0.126) QALYS compared to AC group. The incremental cost per QALY gained is $10,000.	- Open-label trial. - Patients were offered incentive of free hylan G-F 20 to complete the trial. - 95% CI of QALYS among AC + H groups very nearly crosses zero. - Window of 1 year fails to capture downstream costs. - Does not factor in the costs of COX-2 inhibitors, which were not widely available at the time of study.

*AC indicates appropriate care; OA, osteoarthritis; QALY, quality adjusted life year; TKR, total knee replacement.
†Improved = 20% reduction in WOMAC score.

Results of Literature Review on Economics

The published analyses suggest that if the Ontario health system absorbs the cost of hylan G-F 20 treatment, the mean cost to treat a patient with OA of the knee could increase by about $710 (1999 Canadian values). This translates into an incremental cost per quality adjusted life year (QALY) of $10,000. The mean cost per patient to the health system could be substantially reduced if the patient shared the cost of the device.

Ontario-Based Economic Analysis

Notes & Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methodology from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

The dominant competing treatments to 1 year's treatment of hylan G-F 20 are as follows:

- Intra-articular corticosteroids with concomitant analgesic medicine to manage the breakthrough pain (because intra-articular corticosteroids are effective for up to 4 weeks, yet no more than 3 injections a

years are recommended because of safety concerns)
- NSAIDs

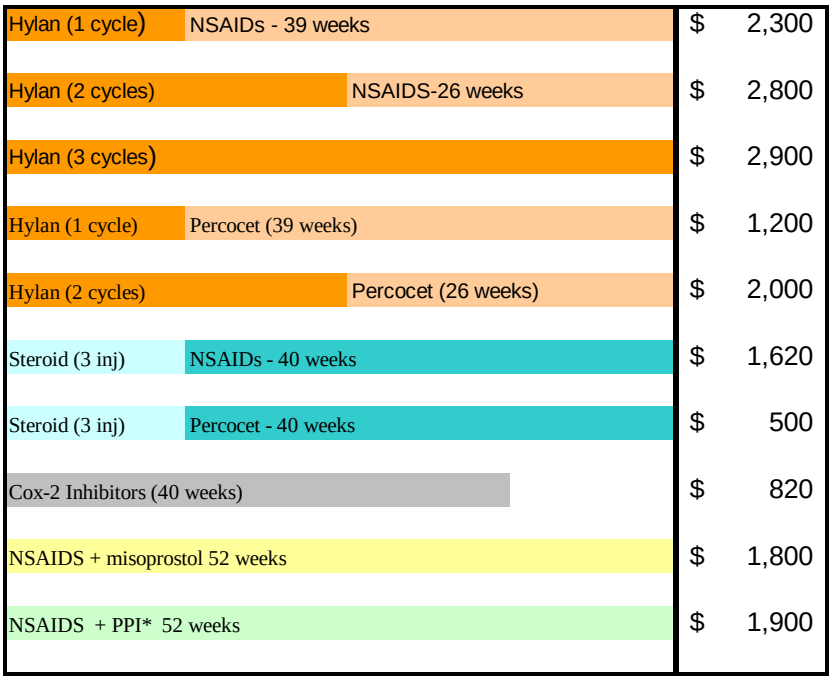
The patient populations of concerns are as follows:

- Ontario residents with OA of the knee who cannot tolerate NSAIDs
- Ontario residents with OA of the knee for whom, for whatever reason, the definitive therapy (i.e., total knee replacement) is not an option
- Patients who are waiting for a total knee replacement
- Patients with mild disease who might use hylan G-F 20 as an adjunct to conventional care

Case-cost estimates

The dominant comparable treatment to intra-articular hylan is intra-articular steroids. According to Ontario Program for Optimal Therapeutics (71) guidelines, no more than 3 steroid shots a year, administered once every 4 months, are recommended. These individuals will also require analgesics for breakthrough pain, because the duration of effect of intra-articular steroids is about 3 weeks. For NSAIDs-intolerant individuals, Percocet (oxycodone and acetaminophen) was modeled as the analgesic option. This choice was based on expert opinion and because sales of oxycodone are escalating in Ontario. The costs include the cost of the device, drugs, and, where relevant, office procedures. Factored into the costs of NSAIDs is the cost of concomitant misoprostol. The cost of the COX-2 inhibitors is provided as a benchmark for comparison. The consumption of COX-2 inhibitors was limited to 40 weeks, because it was felt that patients might take some drug vacations from daily use over a year.

Figure 6. Annual Case-Cost Estimates for Different Treatment Options



*PPI indicates proton pump inhibitor.

Based on these estimates, one treatment course of steroids plus Percocet is the least expensive option. Three cycles of hylan G-F 20 is the most expensive.

A budget impact analysis was conducted to assess the gross and net impact of funding hylan G-F 20 for patients for whom NSAIDs or COX-2 inhibitors were not options. According to unpublished estimates from the Institute for Clinical Evaluative Sciences, consumption of COX-2 inhibitors and NSAIDs has dropped by about 40,000 (22,000 and 18,000 respectively) people in the last 6 months in Ontario. This is likely the consequence of safety concerns. Current health care utilization patterns suggest that about 20% of patients who opt for intra-articular injections receive hylan G-F 20. Using this 20% as an estimate, about 4,500 NSAID-intolerant individuals might receive hylan G-F 20 in lieu of NSAIDs.

This is a conservative estimate, because the estimate of the number of people who have stopped taking NSAIDs is based on a 6-month snapshot and likely exceeds 40,000. Assuming that the range of patients moving from NSAIDs or COX-2 inhibitors to hylan G-F 20 and Percocet lies between 4,500 and 6,750, the gross budget impact would be from $6.8 to $10.3 million (Cdn) The net impact would result in a savings of $300,000 to $400,000 (Cdn), because of the costs saved in lower consumption of NSAIDs and COX-2 inhibitors. However, these figures are based on current patterns of use, which might change should the cost barrier to hylan G-F 20 be removed.

The estimated budget impact of funding hylan G-F 20 as an adjunct to conventional care for 1 year would be $21 million (Cdn) if 10% of NSAID-tolerant patients opted for this treatment, and $63 million (Cdn) if 30% opted for it. These costs take into account the estimated concomitant decrease in annual NSAID use according to the case-cost estimates above. These are conservative estimates, as the entire pool of NSAID-tolerant OA patients (330,000) could opt for this treatment.

A budget impact analysis was not done on the population for whom total knee replacement is indicated, because there is no evidence to support the effectiveness of hylan G-F 20 in this patient population.

Existing Guidelines for Use of Technology

Clinical Guidelines

Ontario

"Intra-articular hyaluronan may provide modest pain relief in mild to moderate OA of the knee. Grade B recommendation." (71)

American

The 2000 update of the American College of Rheumatology (3) reads, "intra-articular hyaluronan therapy is indicated for use in patients who have not responded to a program of nonpharmacologic therapy and simple analgesics; they may be especially advantageous in patients in whom nonselective NSAIDs and COX-2 inhibitors are contraindicated or in whom they have been associated either with a lack of efficacy or adverse events."

European (EULAR)

"There is evidence to support the efficacy of HA in the management of knee OA. However, although pain relief may be obtained for several months, rather than for several weeks as with steroid, this benefit may

be offset by its slower onset of action and by the requirement of a course of 3-5 weekly injections with the logistical and cost issues that entails." (72)

Appraisal/Policy Development

The objective of the policy appraisal is to integrate evidence of effectiveness and safety with need and cost in the Ontario health system context.

Policy Considerations

Patient Outcomes

The best available evidence suggests that older patients (mean age, 71) who are severely disabled and candidates for knee replacement do not benefit from the combination of hylan G-F 20 and acetaminophen. For slightly younger patients (mean age 61) with severe OA pain, no joint effusion, and moderate activity limitation, there's consistent evidence that hylan G-F 20 as an adjunct to conventional care is clinically and statistically superior to placebo, although the magnitude and duration of effect appears to be limited.

Ethics

As a principle of equity, patients afflicted with the pain of OA for whom definitive therapy (i.e., total knee replacement) is not an option should receive support for effective, alternative treatment options.

Demographics

About 750,000 adults in Ontario have OA of the knee. The risk of OA increases with age, particularly after the age of 45 years. About one-half of Ontario adults with OA of the knee seek medical aid. Estimates suggest that only 28,000 (less than 10%) of patients with OA receive intra-articular injections, and that about 20% (5,000) of these are for intra-articular hylan G-F 20. Demand for intra-articular hylan G-F 20 may increase in light of the recent drop in the rate of COX-2 and NSAID inhibitor use, which fell by about 50% between September 2004 and March 2005. About 22,000 Ontario residents stopped taking COX-2 inhibitors over this period, and 18,000 stopped taking NSAIDs.

In addition, about 15,000 Ontario residents either receive or are waiting for a total knee replacement each year. Survey data suggests that at least as many Ontario residents over the age of 55 have OA advanced enough to warrant a total knee replacement, but are unwilling or unable to consider this treatment option.

Diffusion – International, National, Provincial

Hylan G F-20 is a completely or partially insured service in many American and Canadian private health care insurance plans and is an acknowledged, partially insured treatment in European health care systems. The device is not insured in any Canadian provincial health care system, although the office procedure of assessment and administering the injection is covered.

Cost

Most patients who have OA of the knee are aged over 65, are unemployed, and are female. The cost of a course of treatment (i.e., 3 injections) of hylan G-F 20 retails at $448 (Cdn). On average, the magnitude of benefit is clinically significant but small, and the duration of effect appears to be no more than 6 months.

Estimates from the case-costing analysis and published Ontario economic analysis suggest that the mean annual OA-related cost of insuring hylan G-F 20 per patient would be about $700 (Cdn). This translates into an annual cost of $21 million if 10% of the 350,000 people who seek medical care for OA of the knee in Ontario use hylan G-F 20. This would increase tenfold to $210 million if everyone with this disease uses hylan G-F 20.

Stakeholder analysis

Interested patient populations include all Ontario residents with OA of the knee and, in particular, patients for whom the equivalent dominant therapy, NSAIDs, are not an option. The physicians involved in administering hylan G-F 20 include rheumatologists and orthopedic surgeons. Less than 1% of general practitioners administer intra-articular injections.

Because hylan G-F 20 is considered a device and not a drug, because, according to the assessment by Health Canada, it bestows mechanical and not pharmacological activity, it does not qualify for Ontario Drug Benefit status. Consequently, any ministry initiative to improve access to hylan G-F 20 by reducing the cost barrier to the patient might involve a unique funding program.

System pressures

The rate of hylan G-F 20 use is quite low and, according to discussions with the manufacturer, has been stable in Ontario since 1997. Preliminary sales figures indicate that the demand for hylan G-F 20 has not increased since emergent concerns about the safety of COX-2 inhibitors. According to the manufacturer, this is due to general skepticism among physicians about the clinical utility of the device and other devices within the class of hyaluronans. Other barriers include the cost to the patient and that few family physicians (1%) administer intra-articular injections. There may be some pressure within the health care system to offer intra-articular hylan G-F 20 as a solution to reduce wait times for total knee replacement. Nonetheless, there is insufficient evidence to support the idea that hylan G-F 20 defers the need for total joint replacement among patients who are willing to have joint replacement or that it is effective for this population.

Conclusions

When the benefits relative to the risks and costs are considered, NSAIDs and hylan G-F 20 appear comparable (Table 18). Consequently, there's little evidence on which to recommend hylan G-F 20 over NSAIDs, except perhaps for patients who cannot tolerate NSAIDs, although this evidence is indirect, since no studies looked specifically at this population.

Table 18: GRADE of Evidence and Recommendations

Comparison	Magnitude of Benefit	Risk	Cost-burden	Quality	Strength
NSAIDs	Equivalent	Low	Equivalent	Moderate	Weak
Intra-articular steroids	Equivalent	Low	More costly	Moderate	Strong
Other hyaluronans	Equivalent	Low	Equivalent	Low	Weak
Adjunct	Better	Low	More costly	Moderate	Weak

Intra-articular steroids appear to deliver the same risks and clinical benefits as hylan G-F 20 at a lower cost; therefore, there's evidence that intra-articular steroids are the preferred option. Hylan G-F 20 as an

adjunct to conventional care appears to deliver some clinical benefit, although funding hylan G-F 20 as an adjunct would have considerable budget impact, so the benefits of this option do not clearly outweigh the costs. There's some uncertainty about the effect of hylan G-F 20 relative to other hyaluronans, mostly because some of the trials of this comparison were not published.

Many of the studies of hylan G-F 20 have considerable methodological limitations that result in uncertainty about the magnitude of effect. An upcoming review of the evidence by the Osteoarthritis Advisory Panel of clinical experts will likely help to reduce some of this uncertainty.

There is moderate evidence that hylan G-F 20 is no more clinically effective than NSAIDs. The evidence that hylan G-F 20 may be an appropriate option for people with OA of the knee who cannot tolerate NSAIDs is indirect. The possible benefit of fewer cases of NSAID-induced gastropathy in this population must be weighed against the uncertainty of a severe inflammatory adverse reaction to hylan G-F 20. Similarly, there is moderate evidence that hylan G-F 20 is no more clinically effective than intra-articular corticosteroid. The lower cost of intra-articular corticosteroids makes them the preferred option.

There is moderate evidence that hylan G-F 20 is effective as an adjunct to conventional care, delivering a small magnitude of temporary relief at 4 to 26 weeks after treatment. The estimated additional cost to the system of providing hylan G-F 20 as an adjunct to conventional care is about $700 (Cdn) per patient annually. The magnitude and duration of clinical benefit of hylan G-F 20 must be weighed against the uncertainty and potential magnitude of the budget impact (about $35 million to $105 million (Cdn) per year) of funding this device given the high burden of OA in Ontario adults.

There is level 2 evidence that hylan G-F 20 is not effective in people with advanced OA for whom total knee replacement is indicated.

Appendices

Appendix 1: Outcome measures

WOMAC

The WOMAC categories are as follows:

(1) Severity, on average, during specified time interval, of the following:

Pain - Walking
Pain - Stair climbing
Pain - Nocturnal
Pain - Rest
Pain – Weight bearing

(2) Stiffness:

Stiffness occurring in morning
Occurring during the day

(3) Level of difficulty performing the following functions:

Descending stairs
Ascending stairs
Rising from sitting
Standing
Bending to the floor
Walking on flat
Getting in/out of a car
Going shopping
Putting on socks
Rising from bed
Taking off socks
Lying in bed
Getting in/out of bath
Sitting
Getting on/off toilet
Heavy domestic duties
Light domestic duties

The WOMAC parameters are as follows:

0 - none, 1 - mild, 2 - moderate, 3 - severe, 4 - extreme

Lequesne

The Lequesne OA index is an 11-question interview-format questionnaire with 3 sections about `pain or discomfort´ (I), `maximum distance walked and possible necessity of crutches´ (II), and `activities of

daily living´ (III), which are not graded separately. The first section contains 5 questions about `pain or discomfort during nocturnal bedrest´ (IA), `duration of morning stiffness or pain after getting up´ (IB), if `remaining standing for 30 min increases pain´ (IC), `pain on walking´ (ID), `pain or discomfort when getting up from sitting position without the help of arms´ (IE). Questions IC and IE are graded dichotomously: 0 = no, 1 = yes. Questions IA, IB, and ID are graded as follows: `0 = no´, `1 = only on movement or in certain positions´, `2 = without movement´ for IA, `0 = no´, `1 = less than 15 min´, `2 = 15 min or more´ for IB, and `0 = no´, `1 = only after walking some distance´, `2 = early after starting´ for ID.

The second section (II) is graded from `0 = unlimited´ to `6 = less then 100 m´ (`1 = more than 1 km, but limited´, `2 = about 1 km (about 15 min)´, `3 = from 500 to 900 m (about 8-15 min)´, `4 = from 300 to 500 m´, `5 = from 100 to 300 m´, `6 = less than 100 m´). This score is upgraded by 1 point `if the patient uses one walking stick or crutch´ or by 2 points `if the patient uses two walking sticks or crutches´.

The third section (III) assesses difficulty for daily living activities. The questions are: `Can you go up a standard flight of stairs´ (IIIA), `Can you go down a standard flight of stairs´ (IIIB), `Can you squat´ (IIIC), `Can you walk on uneven ground´ (IIID). The score of each question is graded from`0 = without difficulty to `2 = unable to do´ (`0.5 = with some difficulty, `1 = moderate difficulty, `1.5 = great difficulty). The Lequesne OA index is scored as the sum of all questions ranging from 0 to 24.

Additional instruments that measure patient outcome are shown in tabular format below.

Instrument	Description	Score
Knee society clinical rating scale	Combines ratings in the areas of pain, function (gait and functional activities), walking support and range of motion into knee and function scores.	Knee Score: 100 Function score: 100 Interpretation 100: no symptoms or full function 0: extreme symptoms or dysfunction The knee and function scores can be combined or separated.
Lysholm scale	An 8-item questionnaire created to assess symptoms and functional disabilities resulting from a ligamentous injury. All 8 items (pain, instability, locking, stairs, swelling, squat, limp, and support) are aggregated into one score from 0 to 100, where 100 indicates normal knee function. The Lysholm scale is intended to be observer administered, and no patient instructions are provided in the original version.	Pain Instability Locking Stairs Swelling Squat Limp Support Total: 100 Interpretation 100: normal knee 0: extremely abnormal
SF-36	The medical outcomes study 36-item short-form health survey (SF-36) is a widely used measure of general health that comprises 8 subscales: physical	Items Physical functioning: 100 Role-physical: 100 Bodily pain: 100 General health: 100

Instrument	Description	Score
	functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. A score from 0 to 100 is calculated for each dimension.	Vitality: 100 Social functioning: 100 Role-emotional: 100 Mental health: 100 Interpretation 100: best result 0: worst result

Summarizing outcome measures in clinical trials

Two options are available to measure the mean difference in the magnitude of the change in pain of a treatment intervention compared to a control: final VAS pain score and change in VAS pain score from baseline. Either can be used to calculate the weighted mean difference, which is simply the absolute difference between the mean value in the 2 groups of the clinical trials. The 95% confidence interval of this difference can be calculated using the formula:

$$x_i - x_{ii} +/- (1.96) \quad SQRT (s_i/n_i + s/_{ii}n_{ii})$$

Where x_i is the mean of the change from baseline (or mean outcome score) of the treatment group

x_{ii} is the mean of the change from baseline (or mean outcome score) of the control group

s_i is the standard deviation of the change-from-baseline score (or of the mean outcome score) of the treatment group

s_{ii} is the standard deviation of the change-from-baseline score (or of the mean outcome score) of the control group

n_i is the sample size of the treatment group

n_{ii} is the sample size of the control group

Both options are acceptable if the trial is of reasonable size and has been appropriately randomized so that the patients in both arms are comparable in terms of baseline pain. As the Cochrane Handbook for Systematic Reviews of Interventions points out, there is a statistical argument to prefer change-from-baseline outcomes, given that repeated measures made on the same participants (at baseline and after treatment) tend to be correlated, which leads to smaller standard deviations and more precise estimates of treatment effects. However, in order to use change-from-baseline outcomes in meta-analysis, the standard deviations of the change scores must be reported. If they are not, they can be imputed from the mean and baseline scores and their standard deviations provided that the correlation coefficient (R), which ranges between -1 and 1, of these measures can be obtained. The Cochrane Handbook outlines the formula:

$$S(c) = SQRT [s(b)^2 + s(f)^2 – 2 \times R \times s(b) \times s(f)]$$

Where

R is the correlation between the baseline and outcome scores (can range from –1 to 1)

S (c) is the standard deviation of the mean change in score from baseline to final

S (b) is the standard deviation of the mean of the baseline score

S (f) is the standard deviation of the mean of the final score

Summarizing outcomes

The standardized mean difference, often called the effect size, can be used as a summary statistic in meta-

analysis when the trials all assess the same outcome but measure it in a variety of ways. The standardized mean difference expresses the size of the treatment effect in each trial relative to the variability observed in that trial. The method assumes that the differences in standard deviations among trials reflect differences in measurement scales and not real differences in variability among trial populations.

$$\text{SMD} = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}$$

The overall treatment effect can be difficult to interpret, because it is reported in units of standard deviations rather than in units of the scales used. By convention, an effect size of 0.2 to 0.5 is considered small; 0.5 to 0.8, moderate; and greater than 0.8, large. To put a clinical frame of reference on it, clinical trial data suggest the effect of NSAIDs over acetaminophen for the pain of arthritis is small (0.3–0.5), whereas total knee replacements have been estimated to have an effect size of 1.0 to 1.8. {Lo, 2003 19 /id

In order to combine weighted mean differences to generate a summary standardized mean difference, it is important to test for heterogeneity using a statistical calculation that takes into account the different outcomes, sample sizes and variances (i.e. distributions) of the different studies. A popular measure of heterogeneity is I^2, a percentage measure based on Cochrane's Q.

$$I = 100\% \times (Q-df)/Q$$

Q is Cochrane's heterogeneity statistic, and df (degrees of freedom) refers to the number of studies that have been combined to produce the statistics. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. The threshold at which point the studies are too heterogeneous to be combined to produce an overall statistics is a matter of judgment. In general, a value of 75% or higher indicates high heterogeneity, although it is a rather arbitrary designation.

Appendix 2: Licensed Hyaluronans for the Treatment of Osteoarthritis in Canada

Name (Location) of Manufacturer	Licence No.	Device Class	Molecular Weight, kDa	Licence Name	Purpose/Intended Use
Genzyme Biosurgery, a division of Genzyme Corporation (New Jersey, United States)	8394	4	7000	Synvisc (Hylan G-F 20)	Synvisc is a temporary replacement and supplement for synovial fluid. It is intended only for intra-articular use to treat pain associated with osteoarthritis of the knee. A significant change in labeling of the device, revised indications and usage should read: Synvisc is beneficial for all patients in all stages of joint pathology, should not be used in infected or severely inflamed joints, or in patients having skin disease or infections in the area of the injection site.
Anika Therapeutics Inc. (Massachusetts, United States)	957	4	1000–2900	Orthovisc	Orthovisc (sodium hyaluronate for intra-articular injection) is intended as a viscoelastic supplement or a replacement for synovial fluid in human joints. Orthovisc is used to treat the symptoms of human synovial dysfunction, such as osteoarthritis and temporomandibular joint conditions.
Biomet Orthopedics Inc. (Indiana, United States)	18095	3	1000	Fermathron (R)	Fermathron (R) is intended for injection into the synovial space of the knee joint for patients diagnosed with mild to moderate osteoarthritis of the knee.
Q-Med AB (Uppsala, Sweden)	63450	3	1000	Durolane	Durolane is intended for the treatment of osteoarthritis of the knee and is a non-animal stabilized hyaluronan. It is intended for intra-articular injections / a change in the labeling to extend the indication to include treatment of mild to moderate knee and hip osteoarthritis.
Stellar International Inc. **[**	5442	3	1000	Neovisc Sterile Sodium Hyaluronate Solution 1.0%	Produced by streptococcus pyrogen fermentation process; for temporary replacement/replenishment of synovial fluid following arthrocentesis.
Fidia Farmaceutici s.p.a. (Abano Terme [PD], Italy)	30435	4	500–730	Hylagan	Viscous solution of purified hyaluronic acid sodium salt indicated for the sustained relief of pain and joint dysfunction of the knee, hip, and shoulder.
Seikagaku Corporation (Tokyo, Japan)	24358	4	600–1200	Supartz	Supartz is intended for use in the treatment of pain and osteoarthritis of the knee in patients who have failed to respond adequately to

Name (Location) of Manufacturer	Licence No.	Device Class	Molecular Weight, kDa	Licence Name	Purpose/Intended Use
					conservative, nonpharmacologic, and simple analgesics.
Bioniche Pharma Group Ltd.	7730	3	500–730	Suplasyn	Suplasyn is used as a replacement for synovial fluid following arthrocentesis.

Appendix 3: Search Strategy

Hylan Literature Search Strategy – Revised

Search date: February 1, 2005
Databases searched: Ovid MEDLINE, EMBASE, MEDLINE In Process and Not Yet Indexed Citations, Cochrane DSR, CENTRAL, and INAHTA

***Database: Ovid MEDLINE(R) 1966 to January Week 3 2005>**
Search Strategy:
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1. exp Hyaluronan/ (8139)
2. ((hyaluronate adj sodium) or hylan or hyaluronan or hyaluronan).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10930)
3. (Hylan G-F 20 or Synvisc or Hyalgan or Orthovisc or Supartz or Artz or Artzal or BioHY or NASHA or NRD101).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (135)
4. viscosupplementation.mp. (76)
5. or/1-4 (10967)
6. exp Osteoarthritis, Knee/ (2186)
7. exp OSTEOARTHRITIS/ (24474)
8. exp Knee/ (6296)
9. exp Knee Joint/ (25953)
10. 7 and (8 or 9) (4087)
11. 6 or 10 (5660)
12. 5 and 11 (264)
13. limit 12 to (humans and english language) (195)
14. limit 13 to systematic reviews (13)
15. 13 (195)
16. limit 15 to meta analysis (4)
17. 15 (195)
18. limit 17 to (case reports or comment or editorial or letter or "review" or "review literature" or review, multicase or "review of reported cases") (76)
19. 17 not 18 (119)
20. 14 or 16 or 19 (125)
21. from 20 keep 1-125 (125)

*Same strategy used to search Cochrane Central

Database: EMBASE <1980 to 2005 Week 05>
Search Strategy:
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1. exp hyaluronan/ or exp hyaluronan derivative/ (8551)
2. ((hyaluronate adj sodium) or hylan or hyaluronan or hyaluronan).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (10195)
3. (Hylan G-F 20 or Synvisc or Hyalgan or Orthovisc or Supartz or Artz or Artzal or BioHY or NASHA or NRD101).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (349)
4. viscosupplementation.mp. (79)
5. or/1-4 (10284)
6. exp Knee Osteoarthritis/ (2973)
7. exp Osteoarthritis/ (17960)
8. exp knee/ (8937)
9. 7 and 8 (680)
10. 6 or 9 (3557)
11. 5 and 10 (288)
12. exp "Systematic Review"/ (2908)
13. (((systematic review$ or systematic overview$ or systematic$) adj2 search) or handsearch or inclusion criteria or exclusion criteria or meta-analysis or metaanalysis).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (31452)
14. Meta Analysis/ (20256)
15. or/12-14 (33209)
16. 11 and 15 (15)
17. 11 (288)
18. limit 17 to (editorial or letter or note or "review") (77)
19. Case Report/ (824934)
20. 17 not (18 or 19) (203)
21. 16 or 20 (209)
22. limit 21 to (human and english language) (143)

All other databases were searched using a combination of words.

Appendix 4: Jadad Score

Jadad Score Calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?	0/1
Was the study described as double-blind?	0/1
Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct 1 point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.).	0/-1
Deduct 1 point if the study was described as double-blind, but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	

GRADE approach

The GRADE approach permits consideration of 4 key elements: study design, study quality, level of consistency in estimate of effects across studies, and extent of directness (i.e., the extent to which the people, interventions, and outcome measures are similar to those of interest). The GRADE scoring process assigns an initial score (any of high, moderate, low, very low) according to the type of design (e.g., "high" for RCTs, "low" for observational studies, and "very low" for any other evidence). Indications to decrease the grade include: serious (-1) or very serious (-2) limitations to study quality, important inconsistency in the direction and magnitude of effect across studies (-1), some (-1) or major (-2) uncertainty about directness, imprecise or sparse data (-1), and high probability of reporting bias (-1). Indications to increase the grade include: strong evidence of association (i.e. significant relative risk >2.0 based on consistent evidence from two or more observational studies with no plausible confounders (+1), very strong evidence of association (i.e., RR > 5), evidence of a dose-response gradient (+1) or (+1) if all plausible confounders that would have reduced the effect are accounted for. When studies are downgraded on the basis of quality concerns, reviewers must make explicit their reasons.

Once the quality of the evidence has been assessed, the relative magnitude and certainty of the effect is balanced against the level and certainty of risk and burden. If the benefit clearly outweighs the risk and burden with certainty, then a strong recommendation can be made on the basis of the evidence. On the other hand, if the benefit does not outweigh the risk and burden, or if there is uncertainty about the benefit, risk, or burden, then the strength of the recommendation is weaker.

Appendix 5: Randomized Controlled Trials in the Bellamy Review

Description of RCTs of Hylan G-F 20 included in the Bellamy review (*excluded in the Medical Advisory Secretariat's review).

Adams (35){Adams, 1995 105 /id}et al. conducted a 26-week, parallel-group RCT performed at 6 centres in Canada comparing 3 weekly injections of hylan G-F 20 to either NSAID continuation plus 3 weekly control arthrocenteses or NSAID continuation plus 3 weekly injections of hylan G-F 20 in 102 patients with OA of the knee.

*Ardic (45)et al. Conducted an 8-week, placebo-controlled RCT performed at a centre in Turkey comparing 3 weekly injections of hylan G-F 20 to 3 weekly injections of saline in 17 patients with OA of the knee. The authors reported prominent clinical improvement in the hylan G-F 20 group after 8 weeks. No patients reported adverse events. Only safety data are used in the review, because only *P* values are reported for the clinical outcome measures. **Reason for exclusion: Was not identified through the literature search.**

*Auerbach (55)et al. conducted a 1-year, parallel-group RCT performed at a single centre in Germany comparing 3 weekly injections of hylan G-F 20 plus an exercise program to 5 weekly intra-articular injections of gaseous oxygen (3 days per week) plus an exercise program in 111 patients with OA of the knee. Both treatments were effective in relieving pain and improving joint function. Pain relief by hylan G-F 20 and improvement in function by oxygen treatment were shown for more severe levels of cartilage damage. **Reason for exclusion: German language**

*Bayramoglu (50)et al. conducted a 3-month, 3-comparison parallel-group RCT performed at a single centre in Turkey comparing 3 weekly injections of Orthovisc plus a physical therapy program to 3 weekly injections of hylan G-F 20 plus a physical therapy program to a physical therapy program alone (deep tissue heating with short wave diathermy, transcutaneous electrical neuromuscular stimulation and exercises) in 46 patients with OA of the knee. The authors were particularly interested in examining the effect of intra-articular HA injection on muscular strength, testing the hypothesis that if patients were relieved of pain and disability, then indirectly they would build stronger quadriceps muscles. **Reason for exclusion: Difficult to extract primary outcome measure (pain) from the instrument used (Index Severity of the Knee).**

*One RCT included was a comparison of Hyalgan and hylan G-F 20. This trial was discontinued on ethical grounds due to the frequency of acute inflammatory reactions with hylan G-F 20 (21%). No efficacy data were extracted from the abstract. **Reason for exclusion: Was not identified in the literature search. Trial was discontinued.**

Caborn (49)et al. conducted a 26-week, parallel group, single-blind, RCT performed at 14 centres in the United States comparing 3 weekly injections of hylan G-F 20 to 1 intra-articular injection of triamcinolone hexacetonide (Aristospan) in 218 patients with OA of the knee.

Dickson (34)et al. conducted a 12-week, parallel-group, double-blind RCT performed at 18 centres in England and Scotland comparing 3 weekly injections of hylan G-F 20 and dummy capsules taken once daily to either Diclofenac retard 100 mg taken once daily and three weekly arthrocenteses, or dummy capsules taken once daily and 3 weekly arthrocenteses in 165 patients with OA of the knee. According to the authors of the Cochrane review, patients completing the 12-week study, could enter an open-label study in which they received treatment with up to 4additional courses of hylan G-F 20 over a 1-year period.

*Groppa (46)and Moshneaga conducted a 1-year, blinded RCT performed at a single centre in The Republic of Moldova comparing 3 weekly injections of hylan G-F 20 to 3 weekly injections of placebo in 25 patients with OA of knee. Courses were repeated at 6 and 12 months. After the first course, one-third of the patients treated with hylan G-F 20 had less pain and improved joint function compared with none in the placebo group. After 3 courses, 87% of the hylan G-F 20 patients had moderate or very good effect compared with only 20% of the patients in the control group who had moderate effect. No safety data were reported in the abstract. **Reason for exclusion: Was not identified through the literature search.**

Kahan (53)et al. conducted a 9-month, open-label, parallel-group, RCT performed with 81 rheumatologists (21 hospital-based, 60 office-based) in France comparing 3 weekly injections of hylan G-F 20 with conventional treatment in 518 patients with OA of the knee.

Karlsson (44)et al. conducted a 1-year, placebo-controlled, parallel-group, double-blind RCT performed at 19 centres in Sweden comparing 3 weekly injections of Artzal (Astra Lakemedel) to 3 weekly injections of hylan G-F 20 (Roche) and 3 weekly injections of placebo (phosphate-buffered saline solution) in 210 patients with OA of the knee.

Leopold (48)et al. conducted a 6-month, single-blind, parallel-group, RCT performed at a single centre in the United States comparing 3 weekly injections of hylan G-F 20 to 1 injection of betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan), which could be repeated during the study, in 100 patients with OA of the knee. Since the outcome variables had results that were not normally distributed, nonparametric statistical methods were used to analyze the data (e.g., change in median outcomes scores).

*Moreland (38)et al. conducted a 34-week, parallel-group, double-blind RCT performed at 5 centres in the United States comparing 3 weekly injections of hylan G-F 20 to 3 weekly arthrocenteses in 94 patients with OA of the knee. This trial had 2 phases. Phase 1 lasted 10 weeks, after which patients could enter Phase 2, in which all patients received treatment with hylan G-F 20. For this analysis, the Phase 2 data were not included because, although patient blinding was maintained during this phase, treatment was not randomized. Analyses were based on the week-8 evaluation endpoint, which was 2 weeks after the third injection in Phase 1. A statistically significant difference in favour of hylan G-F 20 was detected in overall pain only in a predefined 'flare' population but not in the 'intention-to-treat' population. During the 2 phases, approximately 7% of patients receiving hylan G-F 20 discontinued treatment due to local adverse reactions (pain or swelling) in the injected knee. **Reason for exclusion: Was not identified through the literature search (Abstract only published).**

Raynauld (32)et al. conducted a 1-year, open-label, parallel-group, RCT performed at 14 centres in Canada comparing appropriate care with hylan G-F 20 (AC + H) to appropriate care without hylan G-F 20 (AC) in 255 patients with OA of the knee. For all the primary and secondary effectiveness outcome measures the AC + H group was superior to the AC group. Safety differences favoured the AC + H group. **Medical Advisory Secretariat comment**: **Possibility that prior to randomization subjects were promised free treatment cycle of hylan G-F 20 upon study completion.**

*Scale (42)et al. conducted 2 separate trials. One was a comparison of 2 biweekly injections of hylan G-F 20 versus 2 biweekly injections of saline in 50 patients with OA of the knee. The other was a comparison of 3weekly injections of hylan G-F 20 versus 3 weekly injections of saline in 30 patients with OA of the knee. Both studies were 26-week, parallel-group, double-blind RCTs performed at a single centre in Germany. In the publication, the control arms were combined for the analysis (40 patients). **In the Medical Advisory Secretariat's review, the 2-injection intervention was excluded because a complete treatment course of hylan G-F 20 is 3 injections.**

*The Thompson (52)et al. trial has been published as an abstract. Thompson et al. conducted a 12-week,

parallel-group, double-blind, multicentre RCT in Germany comparing 3 weekly injections of Arthrease to 3 weekly injections of hylan G-F 20 in 321 patients with OA of the knee. The authors reported that both groups had a statistically significant reduction in pain compared to baseline, but there was no between-group difference. With respect to safety, statistically significantly more cases of joint effusion were reported in the hylan G-F 20 group (n = 13) compared to the Arthrease group (n = 1). With respect to methodological quality, it scored 2 out of 5 on the Jadad scale; specific details of randomization and blinding were not reported in the abstract. Allocation concealment was unclear. Biotechnology General (Israel) Ltd. kindly provided the poster of this trial that was presented at the OARSI 2002 Congress as well as an Excel file of the WOMAC pain data. **Reason for exclusion: Published abstract only.**

A publication by Wobig (43)et al. in 1998 conducted the results from a 26-week, parallel-group, double-blind RCT performed at 4 centres in Germany that compared 3 weekly injections of hylan G-F 20 to 3 weekly injections of saline in 110 patients with OA of the knee.

*The 1999 (47)Wobig publication reported the results of 2 arms (hylan G-F 20 versus Artz) of a 4-arm trial (Artz, Healon, hylan G-F 20, nonelastoviscous hylan G-F 20 Nehyl)). This was a 12-week, parallel-group, double-blind RCT performed at 6 centres in Germany comparing 3e weekly injections of hylan G-F 20 to either 3 weekly injections of Artz, 3 weekly injections of Healon, or 3 weekly injections of nonelastoviscous (denatured) hylan G-F 20 in 109 knees. Considering only the published hylan G-F 20 versus Artz comparison, significantly greater pain-relieving effects were detected in favour of hylan G-F 20. No statistically significant differences in the incidence of adverse events between these 2 groups were detected. **The unpublished arms were excluded in the Medical Advisory Secretariat's review. Reasons: Not identified through the literature search. Apparently, details are listed on United States Food and Drug Administration Web site.**

Appendix 6: Additional Trials

The following RCTS were excluded from the literature review of effectiveness, but were included in the review of safety:

The study by Raynauld (65) is the second phase of the randomized pragmatic trial that compared hylan G-F 20 with appropriate care. In the second phase, the comparison was within the hylan G-F 20 arm between patients who received only 1 treatment cycle within the year of observation and those who received more than 1 treatment. The second phase is non-randomized, because the decision to repeat the course of the intervention was left to the discretion of the attending physician and his or her patient.

Waddell (66)is a prospective open-label study of 85 men and women who received a complete treatment of hylan G-F 20 and then requested a second course of treatment, because they were experiencing pain due to OA of the knee pain. The objective of the study was to assess the safety and effectiveness of repeat treatments.

In addition, 8 nonrandomized, noncomparison studies were reviewed (Lussier (57), Lee (58), Wobig (33), Evanich (59)Conrozier (60), Goorman (61), Clarke (62), Bellamy (63). **]** In general, the quality of these studies was poor. The main shortcomings were failure to apply a standardized outcome measure at consistent intervals after treatment and failure to account for cases lost to follow-up.

Only one study was of relatively high quality Wobig (33) It was a multicentre, 12-week, open-label, prospective study of 222 patients. Pre-post measures were administered using a standardized scale (WOMAC), and the authors did an intention-to-treat analysis.

Based on the findings of this study, there is some evidence that hylan G-F 20 reduces pain 12 weeks after treatment and reduces concomitant NSAID use. There is insufficient evidence to draw conclusions about either the magnitude or duration of effect beyond 12 weeks.

Summary of Nonrandomized, Noncomparison Studies

Study	Size	Outcomes Measured	Results	Safety
Lussier (57)	Patients: 336 Knees: 458 Injections: 537	Data extractor converted chart documentation into ordinal scale of improvement; duration of benefit taken from chart; reduction in concomitant medicine; any local or systemic adverse reactions.	Overall Improved: 77% Duration of effect 3–6 months: 22% 6–12 months: 31% Used fewer NSAIDs: 45%	Local: 2.7%/injection Local: 8.3%/patient
Lee (58)	Patients: 74 Knees: 120	Patients reported improvement on ordinal scale at 1 and 12 months, extent of concomitant therapy use and estimated duration of effect.	12 months, overall improved: 91% Duration of effect 3–6 months: 33% 6–12 months: 54% 12 months, used fewer NSAIDs: 24%	Local: 0.8%/injection Local: 4%/patient
Wobig (33)	Patients: 222 Knees: 256 Injections: 758	Powered to detect change in WOMAC-A and VAS from baseline and incidence of adverse events.	12 weeks, V/100 mean change: 35 Symptom free: 39%	Local: 2.5%/injection Local : 8.5%/patient Severe: 1%/patient
Evanich (59)	Patients: 84 Knees: 100	Not powered – just descriptive. Hospital for special surgery knee score used to assess pain and function.	Mean follow-up, 10 months Some improvement: 69% Satisfied: 49% Mean duration: 4.8 months Used rescue therapy: 36%	Local: 16%/patient
Conrozier (60)	Patients: 155 Knees: 172	Outcome measures set by consensus: satisfaction, safety, changes in pain and function.	% Improved on clinical visit Mean lapse 236 days Pain relief: 78% Function: 74% Mean lapse, 461 days % improved on survey Pain relief: 49% Function: 42%	Local: 3.4%/injection 9.3%/knees 10.3%/patient
Goorman (61)	Patients: 84	Pre/post change in SF-36; power calculation not reported.	Change in SF-36 score Baseline 6 months Function: 39 60 Pain: 42 55	Not described
Clarke (62)	Patients: 43	No power calculation; Primary outcome change from baseline in WOMAC A2 (pain on climbing stairs) and patient global assessment.	26 weeks mean change scores Wa2/500: 21.5 (SE, 4.7) Global (% max): 19.7 (SE, 4.9) 52 weeks Significant difference from baseline, yet nearly one-half patients dropped out.	Local: 30%/patients 12%/injections Severe: 4%/injections
Bellamy (63)	Patients: 445 Only 163 (37%) did pre/post tests.	No power calculation; Pre/post change in WOMAC pain, function, and global assessment.	From 3–12 weeks, mean change Wa/20: 4.5 (SE,4.2) Wc/68: 14.2 (SE,14.3)	Not reported

*V indicates VAS; Wa, WOMAC-A for pain; Wc, WOMAC-C for function; Wa2, WOMAC pain on climbing stairs

Quality of Nonrandomized, Noncomparison Studies

	Lussier (57)	Lee (58)	Wobig(33)	Evanich(59)
Design	Retrospective chart review.	Prospective.	Prospective, multisite.	Retrospective.
Sample selection	All patients treated by 5 Canadian physicians. Rationale for selecting clinicians not described.	Consecutive patients in orthopedic clinic.	Characteristics of clinic not described.	Consecutive.
Outcome	Measure of patient improvement not validated; measure of duration of effect not validated.	Standardized measure not used.	Standardized; mean difference from baseline.	Standard pain and function scores reported in chart at time of follow-up. Mean lapse to follow-up was 10 (SD, 4) months.
Intention-to-treat analysis	Proportion of charts with missing data not reported.	Losses to follow-up not reported.	Yes.	14 patients lost to follow-up.
Comments		Magnitude of clinical benefit “improved” unclear.	Arthrocentesis performed.	Significant inverse relationship between effect and grade.
Overall	Poor	Poor	High	Poor

	Conrozier(60)	Goorman (61)	Clarke(62)	Bellamy (63)
Design	Retrospective chart review and patient telephone interview.	Prospective, pre-post comparison.	Prospective, pilot.	Pre-post prospective.
Sample selection	Random sample of 20 records that met inclusion criteria from 10 rheumatologists who agreed to participate.	Consecutive.	Not described, convenience sample, possibly self-selected.	Willing patients of family physicians who trained on injection technique.
Outcome	Instrument not standardized.	Standardized measure and lapse to post-treatment assessment, but clinical relevance of magnitude of change not defined.	Standardized measure.	Standardized measure, but clinical significance of magnitude of change not established.
Intention-to-treat analysis	Unclear; 35/155 (23%) of patients did not complete the questionnaire. It is unclear if this was accounted for in results.	23/84 (27%) patients dropped out; intention-to-treat analysis not reported.	Not done, esp. at 52 weeks when 17/43 patients dropped out.	Analysis conducted on 163 (37%) of 445 patients.
Comments	Retrospective recall of pain duration by patients via telephone interview (mean lapse since first injection, 461 days).	Nearly 30% dropped out and were excluded from the analysis.	Pilot study, likely underpowered.	Very high, unexplained drop-out rate.
Overall	Poor	Poor	Poor	Poor

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