6 2012
1. Jahrgang

OFFPRINT

OUP

Orthopädische und Unfallchirurgische Praxis

Vereinigung Süddeutscher Orthopäden und Unfallchirurgen e.V.
www.vsou.de

J. Heisel, C. Kipshoven

Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee

Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit einer intraartikulären Behandlung der Gonarthrose

VSOU

Deutscher Ärzte-Verlag

Nachdruck – auch auszugsweise –, Vervielfältigung, Mikrokopie, Einspeicherung in elektronische Datenbanken und Übersetzung nur mit Genehmigung der Deutscher Ärzte-Verlag GmbH, 50832 Köln, Postfach 40 02 65

J. Heisel[1], C. Kipshoven[2]

Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee

Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit einer intraartikulären Behandlung der Gonarthrose

Abstract: In a non-interventional study under real-world conditions, 101 patients with long-standing osteoarthritis of the knee (mean age 58 years, ca. 55% female) were treated with three intra-articular (i.a.) injections at weekly intervals of a new medication (high-dose sodium hyaluronate [hyaluronic acid] and sorbitol [GO-ON matrix]*). At the start of treatment, only 4% of the osteoarthritis patients were pain-free, while 21.8% of the patients complained of severe or very severe pain. The proportion of pain-free patients increased steadily after each of the three injections. After the first injection, 16.8% of the patients were pain-free, and 40.6% were pain-free 24 weeks after treatment was initiated. At the same time, the proportion of patients with moderate, severe or very severe pain decreased significantly during treatment. The proportion of patients with severe or very severe pain decreased from 21.8% to 5% after the first injection, and 74.3% of the patients reported that their pain was reduced at 24 weeks after the start of treatment. At the same time, the extent of functional impairment was also reduced. 14.9% of patients complained of severe or very severe impairment before treatment, but only 4% complained of this degree of impairment after the first injection. The proportion of patients with no functional deficit increased from 31.7% to 51.5%. 24 weeks after the start of the injection treatment, 45.5% of patients reported an improvement with respect to baseline values.
The patients and their treating doctors assessed the overall efficacy of the injections in a very similar way. The proportion of patients who reported improvement increased from 64.4% one week after the first injection to 87.1% a week after the third injection, while assessment by the doctors improved from 57.4% to 82.2%. There were no local or systemic adverse effects.

Keywords: Osteoarthritis of the knee, hyaluronic acid, sorbitol, intra-articular injection therapy

Zusammenfassung: In einer nicht-interventionellen Studie unter Praxisbedingungen wurden 101 Patienten mit langjährig bestehender Gonarthrose (ca. 55% weiblich) im Durchschnittsalter von 58 Jahren mit 3 in wöchentlichen Abständen applizierten intraartikulären (i.a.) Injektionen eines neuen Präparates (hochdosiertes Natriumhyaluronat [Hyaluronsäure] und Sorbitol [GO-ON matrix]*) behandelt.
Bei Therapiebeginn waren bezüglich der Gonarthrose nur 4% der Patienten schmerzfrei, während 21,8% der Patienten über starke oder sehr starke Schmerzen klagten. Der Anteil schmerzfreier Patienten nahm nach jeder der 3 Injektionen stetig zu. Schon nach der ersten Injektion waren 16,8% der Patienten schmerzfrei, 24 Wochen nach Therapiebeginn waren es 40,6%. Gleichzeitig nahm der Anteil der Patienten mit mäßiggradigen, starken oder sehr starken Schmerzen unter der Therapie deutlich ab. So fiel bereits nach der ersten Injektion der Anteil an Patienten mit starken und sehr starken Schmerzen von 21,8 auf 5%. 24 Wochen nach Therapiebeginn beurteilten 74,3% der Patienten ihre Beschwerden als gelindert. Zeitgleich verbesserte sich auch das Ausmaß der funktionellen Beeinträchtigung: Nach der ersten Injektion klagten, von anfänglich 14,9%, nur noch 4% der Patienten über starke und sehr starke Beeinträchtigungen. Der Anteil der Patienten ohne funktionelles Defizit nahm von 31,7 auf 51,5% zu. 24 Wochen nach Beginn der Injektionstherapie berichteten 45,5% der Patienten über eine Verbesserung gegenüber dem Ausgangsbefund.
Patienten und behandelnde Ärzte beurteilten die globale Wirksamkeit der Injektionen sehr ähnlich. Der Anteil der Patienten mit berichteter Besserung stieg von 64,4% eine Woche nach der ersten auf 87,1% eine Woche nach der dritten Injektion, die positive Bewertung der behandelnden Ärzte von 57,4 auf 82,2%. Unerwünschte Nebenwirkungen lokaler oder systemischer Art traten nicht auf.

Schlüsselwörter: Gonarthrose, Hyaluronsäure, Sorbitol, intraartikuläre Injektionstherapie

[1] Fachkliniken Hohenurach, Orthopädische Abteilung, Bad Urach
[2] Rottapharm/Madaus GmbH, Köln

* GO-ON matrix distributed by Rottapharm Madaus GmbH is the same product as Synolis V-A developed and manufactured by Anteis SA (Switzerland).

DOI 10.3238/oup.2012.0261-0266

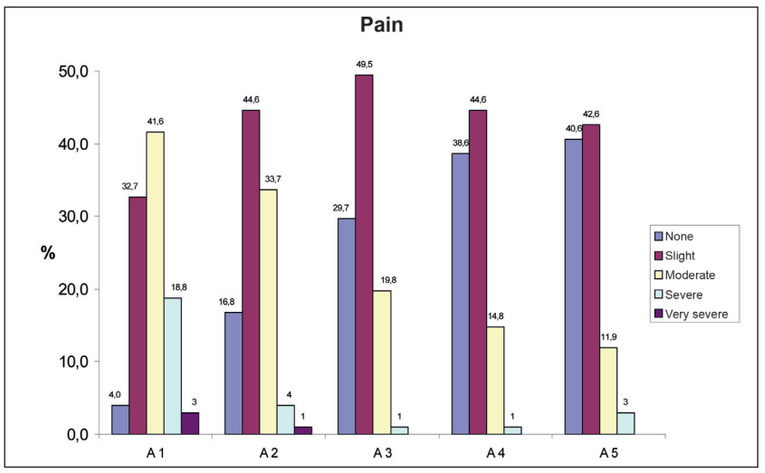

Figure 1 Pain symptoms during the course of treatment. A2: One week after the first injection.

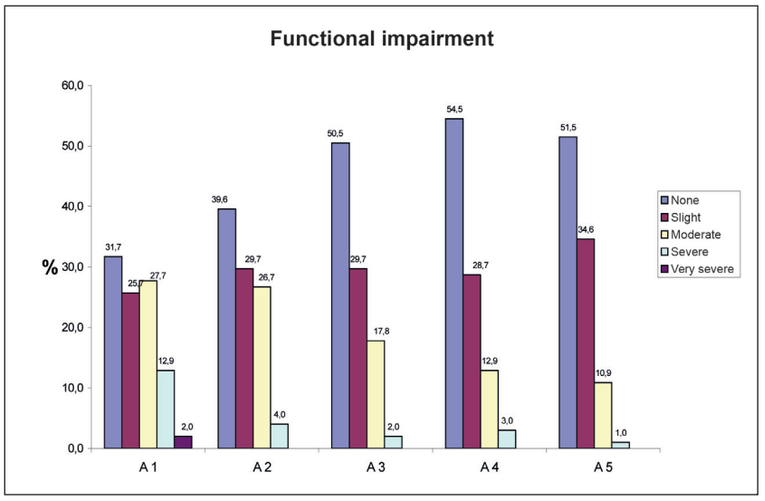

Figure 2 Functional impairment of the affected knee joint during the course of treatment. A2: One week after the first injection.

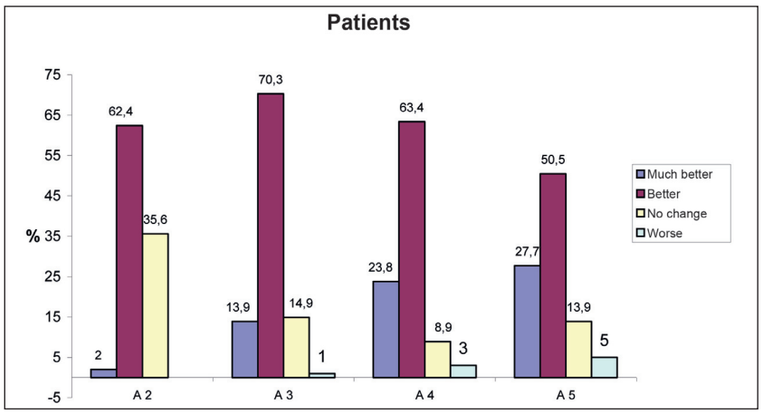

Figure 3 Overall assessment by patients of the efficacy of the intra-articular injection treatment.

Introduction

Osteoarthritis results in progressive and irreversible degenerative changes in synovial joints, starting with the articular cartilage, then attacking the structure of the articulating bones and finally affecting all components of the joint. It occurs most frequently in the knee joint. The most important risk factors for development of osteoarthritis are advanced age and excess biomechanical load due to overweight. Experts estimate that about 10% of people over the age of 50 have clinical osteoarthritis of the knee [1]. A study in the U.S. rated the lifetime risk of symptomatic knee osteoarthritis at 45% [2].

In osteoarthritis, both the viscosity and the quantity of synovial fluid are reduced. This increases friction between the sliding components of the joint and reduces their ability to cushion axial forces, leading to further joint damage. The clinical results are pain and eventually functional impairment of the knee joint.

Hyaluronic acid is a major component of synovial fluid and determines its ability to lubricate the joint. In addition to its viscoelastic properties, preclinical and clinical studies have reported that hyaluronic acid also has chondroprotective [3–6] and anti-inflammatory [5, 7, 8] properties in the joint.

Current trials and recent observational studies on intra-articular injection of various hyaluronic acid preparations (without sorbitol) have demonstrated their clinical efficacy in osteoarthritis of the knee in terms of both pain reduction and functional improvement [9–18]. These positive effects have been confirmed by meta-analysis [19, 20]. Other studies have shown that this treatment is safe and well tolerated [9–11, 14, 16–19]. Intra-articular application of hyaluronic acid is now a recognised treatment option for osteoarthritis of the knee.

Biochemical studies have shown that free radicals have destructive effects on tissues and stimulate inflammatory processes [21, 22]. In the joint, these substances convert hyaluronic acid directly to oligosaccharides, leading to a reduction in viscosity and molecular weight of the synovial fluid [23].

A 1 (Start of study)	• collection of demographic data, duration of osteoarthritis symptoms, concomitant treatment, previous therapeutic measures • self-assessment of current pain and functional impairment by the patients themselves • **first i.a. injection of the preparation**
A 2 (1 week after A 1)	• self-assessment of current pain and functional impairment by the patient • overall evaluation of treatment by patient and doctor • records of any other recent treatment for osteoarthritis • questions regarding side effects and their documentation • **second i.a. injection of the preparation**
A 3 (1 week after A 2)	• as for A 2 • **third i.a. injection of the preparation**
A 4 (1 week after A3)	• as for A 2 (no injection)
A 5 (24 weeks after first injection)	• as for A 2 (no injection) • records of any change in dosage of NSAIDs and analgesics

Table 1 Protocol of the observational study

Pain	A 1	A 2	A 3	A 4	A 5
None (%*)	4	16.8	29.7	38.6	40.6
Slight (%)	32.7	44.6	49.5	44.6	42.6
Moderate (%)	41.6	33.7	19.8	14.8	11.9
Severe (%)	18.8	4	1	1	3
Very severe (%)	3	1	–	–	–
No data (%)	–	–	–	1	2
* Percentage of patients					

Table 2 Pain symptoms during the course of treatment

Sorbitol is known to be an effective scavenger of free radicals. In combination with hyaluronic acid, it acts at two levels. Firstly, sorbitol protects hyaluronic acid from direct attack by free radicals, so that hyaluronic acid stays intact longer as an active agent. Secondly, reducing the concentration of free radicals decreases the migration of macrophages into the synovial membrane, resulting in reduced inflammation and less pain [24].

Materials and Methods

In this prospective non-randomised, non-interventional observational study without a control group, we documented for the first time the clinical course of patients with symptomatic osteoarthritis of the knee who received i.a. injections of high-dose sodium hyaluronate (hyaluronic acid) and sorbitol. The longitudinal study was carried out in a real-world setting. The aim of the study was to gain further knowledge on the efficacy and tolerability of this new preparation in clinical practice. The investigators decided on the indications and patient selection for this treatment. Diagnostic and other therapeutic measures were not affected.

The hyaluronic acid preparation used in this study was 'GO-ON matrix'* (Rottapharm Madaus GmbH). This consists of high doses of sodium hyaluronate with an average molecular

Functional impairment	A 1	A 2	A 3	A 4	A 5
None (%*)	31.7	39.6	50.5	54.5	51.5
Slight (%)	25.7	29.7	29.7	28.7	34.6
Moderate (%)	27.7	26.7	17.8	12.9	10.9
Severe (%)	12.9	4	2	3	1
Very severe (%)	2	–	–	–	–
No data (%)	–	–	–	1	2
* Percentage of patients					

Table 3 Functional impairment of the affected knee during the course of treatment

Change from baseline	A 2	A 3	A 4	A 5
Patients				
Much better (%*)	2	13.9	23.8	27.7
Better (%)	62.4	70.3	63.4	50.5
No change (%)	35.6	14.8	8.9	13.9
Worse (%)	–	1	3	5
Doctors				
Much better (%*)	4	16.8	25.7	29.7
Better (%)	53.5	55.4	56.4	50.5
No change (%)	42.6	27.7	13.9	14.8
Worse (%)	–	–	3	3
* Percentage of patients				

Table 4 Overall assessment by patients and doctors of the efficacy of the intra-articular injection treatment

weight (two million Da) and sorbitol. A 2 ml pre-filled syringe contains 40 mg hyaluronic acid (2% gel), 80 mg of sorbitol and buffered saline. Sorbitol is a free radical scavenger, which not only helps to stabilise hyaluronic acid, but may also accelerate the effects of treatment.

All participants in the study received three intra-articular injections of the preparation into the affected knee joint at intervals of one week. Orthopaedic patients had to be at least 18 years old and have radiologically confirmed osteoarthritis of at least grade I (Kellgren-Lawrence) to be included in the study. Prior indication for treatment with intra-articular hyaluronic acid was required in each case, independent of the planned observational study. Patients were not included in the study if they were receiving (or had received immediately beforehand) another intra-articular treatment (e.g. corticosteroids).

The protocol of the observational study specified five contacts with doctors (A1–A5; Table 1).

The data were analysed using descriptive statistical methods. The mean, median, standard deviation and interquartile ranges were calculated for quantitative variables. Absolute and relative frequencies were calculated for qualitative variables. The principal results are presented graphically.

Results

101 patients with osteoarthritis of the knee (55% women, 45% men) with a mean age of 58.4 years (min.: 15, max.: 88, SD: 12.83) participated in the study. Their mean body weight was 81.7 kg (min: 47, max.: 135, SD: 17.12). Degenerative changes had been present in the knee joints of the patients for an average of 7.5 years (data from 86 patients). The efficacy and tolerability of the treatment were evaluated for all patients.

The most common osteoarthritic complaints or findings at the start of treatment were pain after periods of inactivity in 90.1% of cases, retropatellar pain in 80.2% and a positive Zohlen sign (patellar inhibition) in 75.2%. 41.6% of patients had some joint malposition (mainly misalignment), while 19.8% had joint contracture.

Patients reported physiotherapy (63.4%), NSAID administration (62.4%), topical measures (51.5%) and analgesics (29.7%) as the most common prior treatments. During the course of intra-articular treatment, 12.9% of patients received additional physiotherapy and 6.9% received other forms of non-medicinal therapy.

At the start of the study, only a very small number of patients reported that they had no significant pain, while about one in five patients complained of severe or very severe pain. During treatment with three i.a. injections of hyaluronic acid/sorbitol, the proportion of patients without joint pain increased steadily and continued to increase significantly until 24 weeks after the first injection. At the same time, the proportion of patients with moderate, severe or even very severe pain decreased significantly during treatment. The number of patients in this clinically important group had already decreased significantly after the first injection. Twenty-four weeks after the start of treatment, three quarters of the patients evaluated their pain as alleviated; deterioration was only reported in two cases. The time course of joint pain is shown in Table 2 and Figure 1. Given these results, it is not surprising that concomitant administration of NSAIDs or analgesics could be reduced in 30.7% of patients during the course of treatment.

The proportion of patients without functional impairment of the affected knee joint also increased steadily during the course of treatment. At the same time, the proportion of patients with moderately, severely or very severely restricted movement decreased significantly. Twenty-four weeks after the start of injection treatment, nearly half of the patients showed an improvement compared with baseline parameters. The time course of functional impairment is documented in Table 3 and Figure 2.

Assessments of the overall efficacy of the i.a hyaluronic acid/sorbitol treatment during the study were quite similar for the treating doctors and the patients. 57.5% of doctors and 64.4% of patients already found an improvement one week after the first injection. By the fourth time point, i.e. one week after the third injection, this percentage had increased to 82.1% of doctors and 87.2% of patients. Six months after the start of treatment, i.e. 22 weeks after the last injection, 80.4% of doctors and 78.3% of patients still reported a sustained improvement. Detailed results of the overall assessment of efficacy are summarised in Table 4. The patients' assessment is also shown in Figure 3.

Safety

At each contact with the doctors, patients were asked specifically about adverse events. Any changes in the general condition of the patients, any symptoms and complaints that occurred after the start of injection therapy, and any changes in lab values were noted, and their correlation with the treatment was assessed. There were no findings that could be regarded as undesirable side effects, either as a local reaction at the injection site or as a systemic disorder.

Summary

After three intra-articular injections of the hyaluronic acid/sorbitol preparation, the osteoarthritic knee pain reported by patients (including those with grade 3 osteoarthritis on the Kellgren-Lawrence scale) was significantly reduced in comparison with baseline values. The proportion of pain-free patients was already significant after the first application, and increased steadily after each subsequent dose. At the same time, the proportion of patients with moderate pain decreased continuously after each injection. The number of patients with severe or very severe pain decreased significantly, especially after the first injection. A clear beneficial effect of treatment was still measurable 24 weeks after the first injection.

Function of the affected knee improved in parallel with the pain relief reported by patients.

The efficacy of the intra-articular hyaluronic acid/sorbitol injections was assessed positively by patients and treating doctors in a similar way. The proportion of patients who reported an improvement one week after the third injection was 87%, while the corresponding assessment of the trial doctors was 82%.

No adverse effects of the i.a. hyaluronic acid/sorbitol injections were found during the study.

Conclusion

This observational study was carried out on patients with mostly long-term, symptomatic osteoarthritis of the knee, and demonstrated the efficacy of three intra-articular injections of hyaluronic acid/sorbitol (GO-ON matrix)* in terms of subjective symptoms and impairment of joint function, often after the first injection. Almost nine out of ten patients experienced an improvement after three injections. No adverse effects were reported, either at the injection site or of a systemic nature. In the majority of patients, a positive effect of treatment was still observed six months after the start of therapy. Further prospective studies should be undertaken on a larger patient population to determine the efficacy of this treatment strategy in knee joints with varying degrees of degenerative changes. OUP

Address for correspondence

Prof. Dr. Jürgen Heisel
Senior Consultant, Orthopaedics
m&i Clinics, Hohenurach
Immanuel-Kant-Straße 33
72574 Bad Urach
juergen.heisel@fachkliniken-hohenurach.de

Dr. Christoph Kipshoven
Medical Department
Rottapharm | Madaus GmbH
Colonia-Allee 15
51067 Köln
c.kipshoven@rottapharm-madaus.de

References

1. Günther KP, Merx H. Epidemiologie und sozialmedizinische Bedeutung der Arthrose [Epidemiology and sociomedical importance of osteoarthritis]. In: Zacher J. Herausforderung Arthrose [The Challenge of Osteoarthritis]. Berufsverband der Fachärzte für Orthopädie e.V., 2006: 6–14
2. Murphy L, Schwartz TA, Helmick CG et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008; 59: 1207–1213
3. Dougados M. Sodium hyaluronate therapy in osteoarthritis: arguments for a potential beneficial structural effect. Semin Arthritis Rheum 2000; 30: 19–25
4. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500–730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. Int J Clin Pract 2003; 57: 467–474
5. Moreland LW: Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 2003; 5: 54–67
6. Homandberg GA, Ummadi V, Kang H. Hyaluronan enhances cartilage repair through low grade tissue remodeling involving cytokines and matrix metalloproteinases. Inflamm Res 2004; 53: 534–543
7. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? Semin Arthritis Rheum 2002; 32; 10–37
8. Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakci A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int 2005; 25: 264–269
9. Kemper F, Gebhardt U, Meng T, Murray C. Tolerability and short-term effectiveness of hylan G-F 20 in 4253 patients with osteoarthritis of the knee in clinical practice. Curr Med Res Opin 2005; 21: 1261–1269
10. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol 2006; 33: 951–956
11. Waddell DD, Bricker DC. Clinical experience with the effectiveness and tolerability of hylan G-F 20 in 1047 patients with osteoarthritis of the knee. J Knee Surg 2006; 19: 19–27
12. Turajane T, Tanavaree A, Labpiboonpong V, Maungsiri S. Outcomes of intra-articular injection of sodium hyaluronate for the treatment of osteoarthritis of the knee. J Med Assoc Thai 2007; 90: 1845–1852
13. Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Clin Rheumatol 2008; 27: 975–981
14. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum 2009; 39: 1–9
15. Briem K, Axe MJ, Snyder-Mackler L. Functional and perceived response to intra-articular hyaluronan injection in patients with knee osteoarthritis: persistence of treatment effects over 5 months. Knee Surg Sports Traumatol Arthrosc 2009; 17: 763–769
16. Phiphobmongkol V, Sudhasaneya V. The effectiveness and safety of intra-articular injection of sodium hyaluronate (500–730 kDa) in the treatment of patients with painful knee osteoarthritis. J Med Assoc Thai 2009; 92: 1287–1294
17. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. A randomized, controlled, double-blind, multicenter trial in the Asian population. BMC Musculoskelet Disord 2011; 12: 221
18. Navarro-Sarabia F, Coronel P, Collantes E et al.; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011; 70: 1957–1962
19. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; 2: CD005321
20. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis – meta-analysis. Osteoarthritis Cartilage 2011; 19: 611–619
21. Grootveld M, Henderson EB, Farrell A, Blake DR, Parkes HG, Haycock P. Oxidative damage to hyaluronate and glucose in synovial fluid during exercise of the inflamed rheumatoid joint. Biochem J 1991; 273: 459–467
22. Henrotin Y, Kurz B. Antioxidant to treat osteoarthritis: dream or reality? Current Drug Targets 2007; 8: 347–357
23. Laurent TC. In: Balazs EA (ed) Chemistry and Molecular Biology of the Intercellular Matrix. London: Academic Press, 1970; 2: 703–732
24. Conrozier T, Masson C, Vignon E, Mornand Y, Orset O. Early efficacy of a novel viscosupplement combining hyaluronic acid and sorbitol, ANTI-OX-VS (Synolis) in patients with knee osteoarthritis. ECCEO11, Valencia, 2011, Poster Session I.

Synolis V-A is developed and
manufactured by Anteis S.A. (Switzerland).
www.anteis.com/orthopaedics

SYNOLIS V-A

SODIUM HYALURONATE & SORBITOL VISCO-ANTALGIC

anteis

CHANGE STARTS HERE