Evaluation proposal for the Danish Health Technology Council regarding Arthrosamid for treatment of patients with symptomatic knee osteoarthritis

Instructions for the applicant

This template is used for submitting evaluation proposals to the Danish Health Technology Council in connection with the request of an assessment of new or existing health technology. Evaluation proposals are completed by the applicant and aim to provide the Danish Health Technology Council with a background for launching evaluations. Applicants are recommended to engage in a dialogue with the Danish Health Technology Council's secretariat to receive guidance for proper completion.

The template covers the following main topics:

- Information about the applicant
- Information about the health technology
- Information about the evidence base for the health technology

The Danish Health Technology Council defines health technologies broadly as any use of medical devices, procedures, or processes applied in the treatment or diagnosis of patients. Evaluations of health technologies by the Danish Health Technology Council are always conducted with the consideration of four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics.

Evaluation proposals that are considered by the Danish Health Technology Council will be published on the Danish Health Technology Council's website. If there is confidential information in the evaluation proposal, it must be clearly marked using yellow text highlighting ("example").

The evaluation proposal should be kept as concise as possible and be in either Danish or English. At the end of the document, there is an example of a completed evaluation proposal that applicants can use for inspiration.

If questions arise during the preparation of the evaluation proposal, applicants may contact the Danish Health Technology Council's secretariat for elaboration or clarifications.

In addition to the evaluation proposal, companies, regions, and hospital administrations can complete and include a cost outline that provides an overview of the total costs associated with the use of the health technology. The Danish Health Technology Council's secretariat provides a cost outline template that can be accessed on the Danish Health Technology Council's website.

The completed evaluation proposal is the applicant's product.

Information about the applicant

Name of the applicant (company name or the name of the hospital/region)*:

Contura International A/S.

* If you are a public applicant, the Danish Health Technology Council refers to the requirement that the evaluation proposal in its entirety must be approved by the hospital or regional management.

Contact person (name, position):

Lars Holger Ehlers, managing director at Nordic Institute of Health Economics.

Date of submission of the evaluation proposal:

5th of july 2024.

Information about the health technology

Briefly describe the health technology to be evaluated:

Arthrosamid, also known as injectable polyacrylamide hydrogel (iPAAG), is a health technology designed for the treatment of symptomatic knee osteoarthritis (knee OA) (1). The technology is proprietary 2.5% cross-linked polyacrylamide hydrogel, which is biocompatible and non-biodegradable. After its intraarticular injection iPAAG is integrated into synovium of the joint, which results in long-lasting clinical improvement (1, 4, 6, 7, 8, 9). Clinical effects of Arthrosamid include reduction in pain and stiffness and improvement of physical function, which lasts for at least four years. The purpose of Arthrosamid is to offer a minimally invasive and long-lasting treatment option for patients with symptomatic knee OA who have not achieved sufficient pain relief from other treatment methods such as medication, physiotherapy, or lifestyle changes, and who wish to avoid or delay more invasive procedures like knee surgery (1).

Provide a rationale for why it is relevant to conduct an evaluation of the health technology:

Conducting an evaluation of the health technology Arthrosamid is relevant for several important reasons: 1) Symptomatic Knee OA is a common and disabling condition, affecting approximately 10% of individuals above the age of 55 (1). There are 2 million citizens aged over 55 years according to 2024 data from Statistics Denmark, and therefore there are approximately 200,000 patients with symptomatic knee OA in Denmark. As the population ages, the number of affected individuals is expected to rise, making the need for effective treatment options urgent (2). 2) Existing conservative treatment options for knee OA, such as medications, and physical therapy, have significant limitations (3). Medications have moderate efficacy, short-term effect and side effects, and used mostly in early stages of OA. Physical therapy may not provide sufficient relief. At the same time, surgical interventions are invasive with potential serious complications and intended for patients with advanced OA. Knee arthroplasty presents the last reserve option for a patient with high costs for the healthcare system (3). Thus, Arthrosamid represents a promising solution for the unmet clinical needs in the management of symptomatic mild-to-moderate (Kellgren-Lawrence score 2-3) knee OA, offering an effective, long-lasting, safe, and minimally invasive treatment modality (4).

3) Arthrosamid has proved to be a safe and effective treatment for symptomatic knee OA and could potentially enhance the quality of life for the patients by reducing pain and improving joint function (4). This could enable patients to maintain greater independence and engage more fully in daily activities.
4) An RCT of treatment with Arthrosamid compared to hyaluronic acid (4, 9) concluded that "At 26 weeks after treatment, the effectiveness of Arthrosamid was non-inferior to hyaluronic acid as measured by WOMAC pain subscale. Both products continued to show clinically relevant effectiveness at 52 weeks after treatment as measured by the WOMAC pain, stiffness and physical function subscales and Patient Global Assessment. The effectiveness of Arthrosamid was numerically superior to hyaluronic acid but not statistically significantly different" in the overall study population (4). At the same time, in subpopulations with Kellgren-Lawrence score 2-3, normal BMI or patients below 70 years Arthrosamid was statistically superior to hyaluronic acid (9).

   According to different sources, the efficacy of hyaluronic acid is expected to last for a period from half a year to a year. The Arthrosamid arm of this study tested in a 5-year follow-up has passed a three-year point when Arthrosamid still demonstrated a clinically meaningful and statistically significant improvement vs baseline (4, 9, unpublished material).
5) Arthrosamid is expected to provide economic benefits. The outline of costs (Behandlingsrådets template) shows economic savings per average patient treated with Arthrosamid compared to hyaluronic acid. Savings are mainly related to work hours for rheumatologists and patient time. Currently, two studies with a follow-up period of five years (8, 9) are being conducted. Results are expected ultimo 2024 and 2025. This evaluation will provide insights into the cost savings and cost-effectiveness of Arthrosamid (see below). This information is crucial for healthcare systems that must allocate resources efficiently and justify the adoption of new technologies.
6) Arthrosamid is a labor-saving technology. There will be less workload for rheumatologists in private practice.

In summary, evaluating Arthrosamid will inform healthcare providers, patients, and policymakers, supporting better decision-making and potentially improving treatment outcomes. Arthrosamid could be a cost-effective alternative if its clinical effectiveness and costs are at least comparable to current standard treatments and treatment is associated with savings.

What is the classification of the health technology?

☐Medical device, which is CE marked*

- ☐ Class I
- ☐ Class IIA
- ☒ Class IIB
- ☐ Class III

☐Diagnostic technology, which is CE marked**

- ☐ Class A
- ☐ Class B
- ☐ Class C
- ☐ Class D

☐Procedure (workflow related to diagnostics, treatment, rehabilitation, and/or with a preventive purpose)

If the procedure involves the use of one dominant health technology, describe it, and provide its CE marking and classification

* The Danish Health Technology Council only evaluates medical devices that are CE marked or otherwise meets the legal requirements for medical devices.
** Diagnostic technology utilizing medical equipment for *in vitro* diagnostics.

☒ the applicant hereby declares under penalty of perjury that the above information is accurate and complies with the relevant legislation concerning CE marking.

Briefly describe the current status of the use of the health technology in Denmark and abroad.

In Denmark: Arthrosamid is approved and utilized for the treatment of osteoarthritis in Denmark. It is integrated into clinical practice of private clinics only, due to the lack of reimbursement in the public hospitals. Healthcare providers offer it as an alternative to traditional treatments like hyaluronic acid and steroids. Abroad: Arthrosamid is broadly used in selected European countries such as the UK where its commercialization started earlier. It is gaining recognition internationally and at varying stages of adoption depending on the country.

Proposed PICO specification (Population, Intervention, Comparator, Outcome) for framing the evaluation question:

Population – The patient group in/for which the health technology is utilized and which the evaluation focuses on, including the annual number of patients in Denmark:	The patient population includes individuals experiencing symptomatic knee OA, who have not achieved sufficient pain relief from other treatment methods such as medication, physiotherapy, or lifestyle changes, and who wish to avoid or delay more invasive procedures like knee surgery (and would alternatively be treated with hyaluronic acid).
Intervention – The specific health technology to be evaluated:	The treatment approach under investigation involves an IA injection of Arthrosamid into the affected knee joint.
Comparator – The health technology or treatment that is natural to compare with and currently used as the best and most widely adopted alternative to the intervention in Denmark (I):	The alternative to IA injection of Arthrosamid is injection of hyaluronic acid into the affected knee joint.
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	The patient's physical function, complications, mobility, pain, stiffness, costs, and quality of life/patient global assessment.

* PICO is a tool utilized by the Danish Health Technology Council to formulate precise issues and is crucial in the planning and execution of an evaluation by the Danish Health Technology Council. PICO is further detailed in the Danish Health Technology Council's methods guide, available on the Danish Health Technology Council's website.

Provide a brief description of the proposed comparator and whether the suggested health technology (intervention) is suggested to replace or to be an add on to the current alternative:

Today, there are just a few treatment options available for patients in Denmark with symptomatic knee OA. Treatments aim to alleviate symptoms and prevent the knee OA from getting worse (5) and only partially satisfy the medical needs due to different limitations. Oral painkillers such as paracetamol and ibuprofen are used mostly in the early stages of OA and have limited efficacy. Intraarticular steroids with their good efficacy and fast onset of action have significant side effects and can be used a few times only, so it's not an option for long-term treatment of a chronic condition. Orthobiologic therapies such as stem cell treatments or platelet-rich plasma (PRP) are in different stages of development and their efficacy does not have enough clinical evidence yet (15). Arthrosamid has been investigated in a clinical trial against hyaluronic acid since it is the best existing and widely implemented alternative to Arthrosamid treatment. The injections with hyaluronic acid are commonly used to alleviate symptoms and provide temporary relief by reducing irritation and swelling of the joint lining (providing viscosupplementation) (3). Hyaluronic acid injections are administered once a week for 3-5 weeks, and if there is no improvement after three injections, further treatment is not expected to be effective (3). Although this can be effective, it needs to be administered again after six months as it dissipates from the body (3). Arthrosamid is suggested as an alternative/replacement for hyaluronic acid, offering a different mechanism of action with potentially longer-lasting effects and higher efficacy in patients with Kellgren-Lawrence score 2-3 (4, 9).

Is the health technology mentioned in professional clinical guidelines from institutions like the Danish Health Authority or medical scientific societies? Specify which ones:

At present, there are no existing clinical guidelines for the utilization of Arthrosamid in Denmark or internationally.

Has the health technology been evaluated by other HTA institutions (e.g. NICE, Nye Metoder)? Specify which ones:

Arthrosamid has not been evaluated by other HTA institutions, and therefore there are no published or available health technology assessments.

Provide the names of manufacturers/suppliers of the health technology, if relevant:

Contura International A/S.

Information about the evidence base for the health technology:

Indicate whether the health technology (compared to the current alternative) aims to improve treatment/diagnosis of the patient group as perceived from one or more of the following perspectives (indication of the primary impact of using of the health technology):

☒ Clinical effectiveness and safety

☒ Patient preferences and experiences

☒ Organizational aspects, such as changes to workflows	☒ Costs associated with treatment/diagnostics

*For the evaluation of health technologies, the Danish Health Technology Council employs four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics. For further elaboration on these perspectives, refer to the Danish Health Technology Council Council's methods guide for the evaluation of health technologies, available on the Danish Health Technology Council Council's website.

State the expected impact of the health technology within the indicated perspectives above:

Clinical effectiveness and safety:
- Decrease knee pain and stiffness.
- Improves patient's physical function and patient global assessment (PGA).

Patient preferences and experiences:
- Improves health related quality-of-life.

Organizational aspects:
- Treatment with Arthrosamid could reduce the number of physician visits compared to current treatment with hyaluronic acid.

Costs associated with treatment/diagnostics
- Treatment with Arthrosamid is cost-reducing compared to treatment with hyaluronic acid and is therefore expected to be a cost-effective alternative.

Provide references* for documentation of the health technology's effects (if possible, include up to 2 key references per perspective):

Clinical effectiveness and safety	- Bliddal, H., Overgaard, A., Hartkopp, A., Beier, J., Conaghan, P.G., Henriksen, M., 2021. Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: A 6 Months Prospective Study. J Orthop Res Ther 6, 1188 (1). - Bliddal, H., Overgaard, A., Hartkopp, A., Beier, J., Conaghan, P.G., Henriksen, M., 2021. Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results of a 52 Week Prospective Study. Osteoarthritis and Cartilage 29, S278 (6). - Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2022. A Prospective Study of Polyacrylamide Hydrogel for Knee Osteoarthritis: Results From 2 Years After Treatment. Osteoarthritis and Cartilage 30, S371-S372 (7). - Henriksen, M., Beier, J., Hartkopp, A., Conaghan, P.G., Bliddal, H., 2023. 3 year results from a prospective study of polyacrylamide hydrogel for knee osteoarthritis. Osteoarthritis and Cartilage 31, P682-3 (8). - Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2022. One-Year Performance of Polyacrylamide Hydrogel vs. Hyaluronic Acid: A Randomised Controlled Study. Osteoarthritis and Cartilage 30, S370-S371 (4). - Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2023. Polyacrylamide hydrogel versus hyaluronic acid in knee osteoarthritis: a subgroup analysis of a randomized study. Orthopaedic Proceedings 105-B(SUPP 13):81 (9).

	- Henriksen, M., Overgaard, A., Hartkopp, A., Bliddal, H., 2018. Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee osteoarthritis: an observational proof-of-concept cohort study. Clinical and experimental rheumatology 36, 1082 (10). - Overgaard, A., Bliddal, H., Henriksen, M., 2019. Safety of Intra-Articular Polyacrylamide Hydrogel for the Treatment of Knee Osteoarthritis Symptoms: A Retrospective Case Series. Clin Ortho Adv Res J: COARJ-100001 (11). - Christensen, L., Daugaard, S., 2016. Histological Appearance of the Synovial Membrane after Treatment of Knee Osteoarthritis with Polyacrylamide Gel Injections: A Case Report. Journal of Arthritis 5, 217 (12). - Maulana, R., Cole, A., Lee, P.Y.F., 2022. Reduction in Patellofemoral Bone Marrow Lesions Following Single Arthrosamid Intra -Articular Injection of Polyacrylamide Hydrogel (ipaag) in the Treatment of Advanced Osteoarthritis. J Arthritis 11, 24-26 (13). - Cole, A., Maulana, R., Whitehead, J.P., Lee, P.Y.F., 2022. A Systematic Review of the Novel Compound Arthrosamid Polyacrylamide (PAAG) Hydrogel for Treatment of Knee Osteoarthritis. Medical Research Archives [online] (14).
The Patient perspective	- Unpublished material on patient satisfaction, no comparison, one arm.
Organizational Implications	
Health Economics	- Unpublished data. [redacted] - The outlines of cost using the template from Behandlingsrådet.

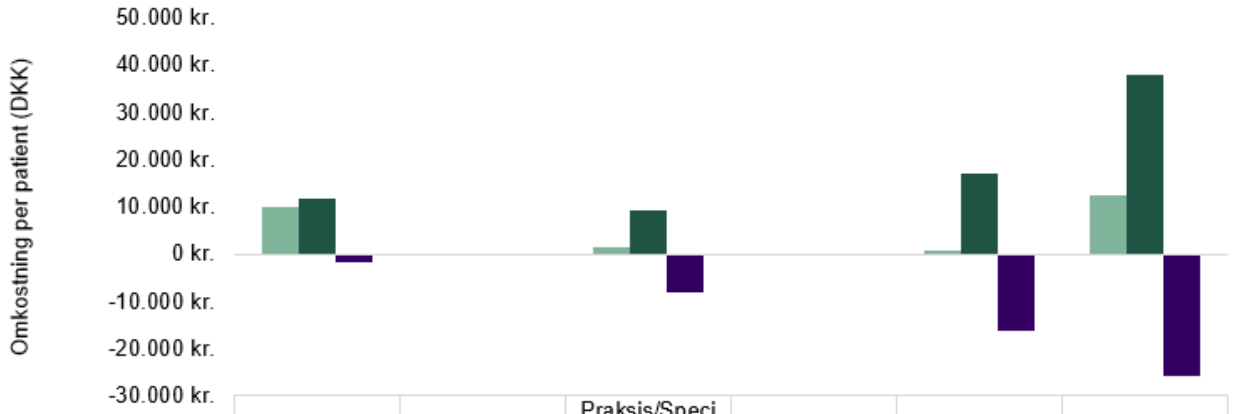
* Reference to published, ongoing, or unpublished data.

Indicate whether the health technology is expected to incur additional costs, cost reductions, or be cost-neutral compared to the current alternative. Briefly describe how the costs are expected to be distributed across sectors (hospital, general practice, municipalities, patients, etc.), and what is considered to drive the potential addition or reduction in costs. The Danish Health Technology Council encourages applicants to complete and include the Danish Health Technology Council's cost outline, accessible on the Danish Health Technology Council's website.

☐ Additional costs ☒ Cost reductions ☐ Cost-neutral

[redacted]

	Teknologi	Hospital	Praksis/Speciall.	Kommune	Patient	Sum
Sundhedsteknologi	10.000 kr.	0 kr.	1.457 kr.	0 kr.	846 kr.	12.304 kr.
Alternativ	11.733 kr.	0 kr.	9.381 kr.	0 kr.	16.929 kr.	38.043 kr.
Difference	**-1.733 kr.**	**0 kr.**	**-7.924 kr.**	**0 kr.**	**-16.083 kr.**	**-25.740 kr.**



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[redacted]

Free-text field (optional additional information, max 300 words):

Please note that we find it of utmost importance to be able to include unpublished data. We will follow the Danish treatment council's principles for use of unpublished data.

References:

1. Bliddal, H., Overgaard, A., Hartkopp, A., Beier, J., Conaghan, P.G., Henriksen, M., 2021. Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: A 6 Months Prospective Study. J Orthop Res Ther 6, 1188.
2. Danmarks Statistik. NYT: Markant flere ældre i fremtiden [Internet]. [cited 2024 Jun 13]. Available from: https://www.dst.dk/da/Statistik/nyheder-analyser-publ/nyt/NytHtml?cid=26827
3. Sundhed.dk. Artrose, knæ - Lægehåndbogen på sundhed.dk [Internet]. [cited 2024 Jun 13]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/ortopaedi/tilstande-og-sygdomme/knae/artrose-knae/
4. Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2022. One-Year Performance of Polyacrylamide Hydrogel vs. Hyaluronic Acid: A Randomised Controlled Study. Osteoarthritis and Cartilage 30, S370-S371.
5. Sundhed.dk. Slidgigt i knæet (knæartrose) - Patienthåndbogen på sundhed.dk [Internet]. [cited 2024 Jun 13]. Available from: https://www.sundhed.dk/borger/patienthaandbogen/knogler-muskler-og-led/sygdomme/knae/slidgigt-i-knaeet-knaeartrose/

6. Bliddal, H., Overgaard, A., Hartkopp, A., Beier, J., Conaghan, P.G., Henriksen, M., 2021. Polyacrylamide Hydrogel Injection for Knee Osteoarthritis: Results of a 52 Week Prospective Study. Osteoarthritis and Cartilage 29, S278.
7. Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2022. A Prospective Study of Polyacrylamide Hydrogel for Knee Osteoarthritis: Results From 2 Years After Treatment. Osteoarthritis and Cartilage 30, S371-S372.
8. Henriksen, M., Beier, J., Hartkopp, A., Conaghan, P.G., Bliddal, H., 2023. 3 year results from a prospective study of polyacrylamide hydrogel for knee osteoarthritis. Osteoarthritis and Cartilage 31, P682-3.
9. Bliddal, H., Beier, J., Hartkopp, A., Conaghan, P.G., Henriksen, M., 2023. Polyacrylamide hydrogel versus hyaluronic acid in knee osteoarthritis: a subgroup analysis of a randomized study. Orthopaedic Proceedings 105-B(SUPP 13):81
10. Henriksen, M., Overgaard, A., Hartkopp, A., Bliddal, H., 2018. Intra-articular 2.5% polyacrylamide hydrogel for the treatment of knee osteoarthritis: an observational proof-of-concept cohort study. Clinical and experimental rheumatology 36, 1082
11. Overgaard, A., Bliddal, H., Henriksen, M., 2019. Safety of Intra-Articular Polyacrylamide Hydrogel for the Treatment of Knee Osteoarthritis Symptoms: A Retrospective Case Series. Clin Ortho Adv Res J: COARJ-100001
12. Christensen, L., Daugaard, S., 2016. Histological Appearance of the Synovial Membrane after Treatment of Knee Osteoarthritis with Polyacrylamide Gel Injections: A Case Report. Journal of Arthritis 5, 217
13. Maulana, R., Cole, A., Lee, P.Y.F., 2022. Reduction in Patellofemoral Bone Marrow Lesions Following Single Arthrosamid Intra -Articular Injection of Polyacrylamide Hydrogel (ipaag) in the Treatment of Advanced Osteoarthritis. J Arthritis 11, 24-26
14. Cole, A., Maulana, R., Whitehead, J.P., Lee, P.Y.F., 2022. A Systematic Review of the Novel Compound Arthrosamid Polyacrylamide (PAAG) Hydrogel for Treatment of Knee Osteoarthritis. Medical Research Archives [online].
15. DanskReumatologi.dk. National behandlingsvejledning: Artrose [Internet]. [cited 2024 Jun 26]. Available from: https://danskreumatologi.dk/nbv/sygdomme/national-behandlingsvejledning-nbv-artrose/