Consolidated stakeholder feedback

HTA report

Intra-articular glucocorticoid injections for osteoarthritis of the hip or knee

Stakeholders (SH; in alphabetical order) that have provided comments:

1	Mepha Pharma AG
2	Santésuisse
3	Schweiz. Ges. für Physikalische Medizin und Rehabilitation (SGPMR)
4	Schweizerische Gesellschaft für Rheumatologie (SGR)
5	Swiss Orthopaedics

SH	SH comment	Reply authors / BAG
1	1. We acknowledge the well applied methodology in this HTA. However, the implications of this HTA remain unclear. The reimbursed IAGI preparations including Mephameson are inexpensive and, as stated in the HTA report, cost-effective. 2. IAGI are well established in clinical practice, and the WZW criteria have been reviewed multiple times by the triennial BAG reviews. 3. Moreover, Mephameson as an intra-articular injection is usually used in inpatient treatment setting as secondary therapy option when patients have not responded to oral or topical analgesics. Therefore, we do not see the need to change the reimbursement conditions or to limit the use of IAGI.	1. The HTA findings indicate that the role of IAGI likely lies in the short-term management of pain (i.e. favorable effects evident at 1 month after treatment, but not at 3 months) in patients with hip and knee osteoarthritis (OA), and that single injections have limited utility for long-term management of symptoms. As noted by the stakeholder, the HTA also suggests IAGI is likely to be cost-effective in patients with knee OA (hip was not modelled), noting there was substantial uncertainty in the modelled results. 2. The strength of the HTA lies in the robust systematic clinical evaluation, de novo cost-effectiveness analysis and budget impact assessment. It provides an in-depth appraisal of the evidence as it relates to the Swiss health care context. 3. Noted, thank you for the feedback. IAGI was examined as an adjunct to standard care, i.e. in combination with analgesics, in the economic evaluation.
2	1. The comprehensive HTA report is clear and well structured. Information on the causes, risk factors, pathology, diagnosis and progression of OA of the knee and hip is presented in a comprehensible manner. Research questions, PICO criteria and methodological approaches are presented transparently.	1. Noted, thank you for the feedback. 2. After initially considering the inclusion of systematic reviews, it was decided to conduct a de novo evaluation because the most comprehensive systematic review was published in 2015 by the Cochrane collaboration (Juni 2015). However, 8 RCTs have been published since. Also, 11 of the RCTs included in the Juni 2015

	2. However, the reason for a protocol deviation in the HTA phase with a decision for a clinical de novo evaluation and exclusion of systematic reviews is not completely understandable. 3. While the mechanism of action and administration of IAGI are described in detail, there is only isolated information about other non-surgical treatment options for OA and their combinations (e.g. physiotherapy, medication, weight loss, training, etc.). This is surprising given that international guidelines recommend IAGI as one of several therapeutic options (e.g. ACR, EULAR, ESCE, etc.). The isolated study of the IAGI without taking into account the treatment algorithm and therapeutic phases as well as other factors (e.g. duration of symptoms, previous and accompanying treatments, etc.) cannot adequately capture the importance of the IAGI in OA, reduces the significance of the results and makes their interpretation more difficult in the treatment context. 4. Several methodological limitations (e.g. mostly small numbers of cases, sometimes different or unknown degrees of KL, concomitant medication, wash-out pretreatment, indication for IAGI, etc.) as well as their significance for the interpretation of the results (e.g. heterogeneity, sometimes limited transferability, etc.) are mentioned and partly discussed. 5. The statements on the economic assessment of the IAGI can be understood. 6. In summary, it can be said that the report is a basis for limiting the performance. Original German language feedback: Der umfassende HTA-Bericht ist übersichtlich und gut strukturiert. Angaben zu Ursachen, Risikofaktoren, Pathologie, Diagnostik und Verlauf der OA von Knie und Hüfte werden nachvollziehbar aufgezeigt. Forschungsfragen, PICO-Kriterien und methodische Vorgehensweisen sind transparent dargestellt. Die Begründung für eine Protokoll-Abweichung in der HTA-Phase mit Entscheid für eine klinische de-novo Evaluation und Ausschluss von Systematischen Reviews ist jedoch nicht vollständig nachvollziehbar. Während Wirkungsmechanismus und Verabreichung der IAGI detailliert beschrieben werden, finden sich zu weiteren nicht-chirurgischen Behandlungsoptionen der OA sowie deren Kombinationen (z.B. Physiotherapie, Medikamente, Gewichtsreduktion, Training etc.) nur vereinzelte Hinweise. Dies erstaunt insofern, als internationale Guidelines die IAGI als eine von mehreren therapeutischen Optionen empfehlen (z.B. ACR, EULAR, ESCE etc.). Die isolierte Untersuchung der IAGI ohne Berücksichtigung von Behandlungs-Algorithmus und therapeutischen Phasen sowie von weiteren Faktoren (z.B. Beschwerdedauer, Vor- und Begleitbehandlungen etc.) vermögen den Stellenwert der IAGI bei OA nur ungenügend zu erfassen, vermindern die Aussagekraft der Ergebnisse und erschweren deren Interpretation im Behandlungskontext. Mehrere methodische Einschränkungen (z.B. meist kleine Fallzahlen, teilweise unterschiedliche oder unbekannte KL-Grade, Begleitmedikation, Wash-out Vorbehandlung, Indikation für IAGI etc.) sowie deren Bedeutung für die Interpretation der Ergebnisse (z.B. Heterogenität, teilweise eingeschränkte Übertragbarkeit etc.) werden genannt und teilweise diskutiert. Die Ausführungen zur ökonomischen Beurteilung der IAGI können nachvollzogen werden.	review were not applicable to our research question. Additionally, our methodology included a longitudinal meta-analysis, therefore a de novo review was considered necessary. 3. To determine the therapeutic action of IAGIs in patients with knee and hip OA it is necessary to examine RCTs that ideally compare IAGIs in isolation, or that treatment and control groups are restricted to the same level of physiotherapy and adjunct medications, so that the only variable is IAGI, otherwise it would be impossible to attribute causation when multiple treatments are used. It is an inherent limitation with RCTs that their design is simplified and doesn't reflect the more complex treatment algorithms proposed by different country or region-specific guidelines. However, the significance of these variables (except drugs) on the outcomes of IAGI is questionable since they do not affect the pharmacokinetics or pharmacodynamics of IAGI. In regard to the absence of active-controlled trials in the HTA, this decision was made due to discordance in international clinical practice guidelines and local expert feedback around the recommended alternatives to IAGI for the treatment of hip and knee OA. Therefore, a decision was made in consultation with the FOPH to limit the scope of the evaluation to the efficacy of IAGI (i.e. compared to placebo or sham), noting that this does pose limitations on the findings of the HTA as noted here by the stakeholder. 4. Noted. Risk of bias was assessed using the better-known variables (that were reported and extractable) that have the potential to bias the findings. All those items listed in point 4 are valid concerns for which the impact is not known, but do have the potential to introduce confounding variability. 5. Noted, thank you for your feedback. 6. Noted, thank you for your feedback.

	Zusammenfassend kann festgehalten werden, dass der Bericht eine Grundlage für eine Limitation der Leistung ist.	
3	1. The SGPMR welcomes the HTA initiative on 'intra-articular glucocorticoid injection' (IAGI). 2. The results of the present HTA correspond to the practices as set out in various international guidelines for gonarthrosis and coxarthrosis. 3. The IAGI effect is short-lasting. IAGI can replace other therapy modalities (see cost-effectiveness). The level of knowledge about IAGI is modest. 4. From a clinical perspective, the SGPMR should add that the indication for IAGI plays a central role, with more experienced specialists likely to perform better. In a situation known for decades as "activated osteoarthritis", clinical experience shows that the IAGI effect is better with increased synovial fluid than with "dry" joints, which should urgently be investigated in a study. On the other hand, chronic pain patients are not suitable for IAGI. Unfortunately, such considerations have no place in an HTA, but are likely to become more important as medicine becomes increasingly personalized. 5. In summary, there is nothing to add to the present HTA on IAGI and its known results. Original German language response: Die SGPMR begrüsst die HTA-Initiative zur 'intra-articular glucocorticoid injection' (IAGI). Die Ergebnisse der vorliegenden HTA entsprechen den Gepflogenheiten, wie sie in verschiedenen internationalen Guidelines für Gon- und Coxarthrose festgehalten sind. Die IAGI-Wirkung ist kurzdauernd. IAGI können andere Therapiemodalitäten ersetzen (siehe cost-effectiveness). Der Wissensstand zur IAGI ist bescheiden. Aus klinischer Sicht seitens der SGPMR soll angefügt werden, dass der Indikation für eine IAGI die Hauptrolle zukommt, wobei erfahrenere Spezialistinnen und Spezialisten besser abschneiden dürften. Bei einer unter dem Stichwort "aktivierte Arthrose" seit Jahrzehnten bekannten Situation betätigt die klinische Erfahrung, dass die IAGI-Wirkung bei vermehrter Gelenksflüssigkeit besser ist als bei "trockenem" Gelenk, was dringend in einer Studie untersucht werden sollte. Hingegen eignen sich chronische Schmerzpatientinnen und Schmerzpatienten nicht für eine IAGI. Solche Überlegungen haben leider in einem HTA keinen Platz, dürften aber mit zunehmend personalisierter Medizin an Bedeutung gewinnen. Zusammengefasst ist der vorliegenden HTA zur IAGI und ihren bekannten Ergebnissen nichts beizufügen.	1. Noted, thank you. 2. Noted, thank you. 3. Noted, thank you. 4. The RCTs included in this analysis did not differentiate between 'dry' joints and 'activated arthrosis/ activated osteoarthritis' commonly referred to as a 'flare'. However, if some enrolled patients were experiencing a flare then they should have at least been randomised evenly between treatment and control groups. But if the dominant group of patients were 'dry' cases then they would, potentially, influence the results and negate any benefit in 'activated OA' (assuming the assertion that activated arthrosis responds more favorably to IAGI than 'dry' OA). However, this is hypothesizing and we do not have convincing data to substantiate or refute this claim. 5. Noted, thank you for the feedback.
4	1. We acknowledge the thorough search and the very careful, technically excellent evaluation of the sparse available scientific data on which the assessment attempt was based. 2. As already stated during the stakeholder consultation, infiltrating painful joints alone is not common practice in Switzerland; Almost only "activated" arthroses are infiltrated, with or without joint effusion. The study populations used in the HTA therefore do not correspond to the patients who are infiltrated in everyday clinical practice in Switzerland. 3. As expected, the sub-analyses used in the HTA are not sufficient to make valid statements about	1. Thank you for your feedback. 2. Thank you for your feedback. It is acknowledged that patients in the RCTs did not consistently meet the criteria for "activated OA". Some studies focused on specific subgroups (e.g., joint effusion), but important factors like varus and valgus malalignment, meniscus damage, or bone marrow edema were not systematically evaluated. Therefore, the overall estimates do have applicability concerns, which are represented in the GRADE appraisals of the certainty of evidence, and highlighted in section 10.2 on limitations in the clinical analysis. 3. Generalisability is one element of evidence synthesis, along with risk of bias, imprecision, inconsistency and other factors that contribute to the overall certainty of evidence. It should be noted, however, that all relevant

	the effectiveness or benefit of patients treated in Switzerland. 4. In the economic evaluation, the specified narrow range of total costs suggests that the estimate is too reliable. The reliability of the data obtained from just one insurer and not characterized in any more detail in the report must be questioned, as mentioned in the limitations. 5. In particular, it remains unclear how the total numbers of annual infiltrations were obtained. A large proportion of the joint infiltrations carried out in everyday clinical practice are carried out for arthritis; It remains unclear how such infiltrations were differentiated from those in osteoarthritis. It contradicts everyday experience that the number of hip injections performed accounts for more than half of the knee injections. 6. Last but not least, it should be pointed out that the costs of the individual injection have been estimated incorrectly or far too high: When it comes to knee infiltrations, the proportion of sonographically controlled interventions in practice is significantly lower than estimated by only three experts. Above all, the TARMED positions 39.3700 and 39.3710 must not be cumulated with 24.0130 and 24.0140, respectively! Accumulation with 00.1190 is also not permitted. 7. Overall, the uncertainty regarding the estimated benefit in HTA for Swiss patients remains high. Original German language response: - Wir anerkennen die gründliche Suche und die sehr sorgfältige, technisch hervorragende Auswertung des spärlichen verfügbaren wissenschaftlichen Datenmaterials, welches dem Versuch des Assessments zugrunde gelegt wurde. - Wie bereits bei der Stakeholder-Konsultation mitgeteilt, entspricht das Infiltrieren von alleinig schmerzhaften Gelenken nicht der gängigen Praxis in der Schweiz; es werden fast nur «aktivierte" Arthrosen infiltriert, mit oder ohne Gelenkerguss. - Die im HTA herangezogenen Studienpopulationen entsprechen somit nicht den Patienten, die in der Schweiz im klinischen Alltag infiltriert werden. - Die im HTA verwendeten Subanalysen sind erwartungsgemäss nicht ausreichend, um valable Aussagen zur Wirksamkeit bzw. zum Nutzen der in der Schweiz behandelten Patienten zu treffen. - Bei der ökonomischen Evaluation suggeriert die angegebene enge Bandbreite der Gesamtkosten eine zu hohe Reliabilität der Schätzung. Die Zuverlässigkeit der von nur einem einzigen Versicherer bezogenen und im Bericht nicht näher charakterisierten Daten ist wie in den Limitationen erwähnt zu hinterfragen. Insbesondere bleibt offen, wie die Gesamtzahlen der jährlichen Infiltrationen gewonnen worden sind. Ein grosser Teil der im klinischen Alltag durchgeführten Gelenkinfiltrationen erfolgt bei Arthritiden; es bleibt offen, wie solche Infiltrationen von jenen bei Arthrose abgegrenzt worden sind. Es widerspricht der Alltagserfahrung, dass die Anzahl der durchgeführten Hüftinjektionen mehr als die Hälfte der Knieinjektionen ausmacht. Nicht zuletzt soll darauf hingewiesen werden, dass die Kosten der einzelnen Injektion falsch bzw. viel zu hoch geschätzt worden sind: Bei den Knieinfiltrationen ist der Anteil der sonographisch gesteuerten Interventionen in der Praxis deutlich niedriger als von den nur drei Experten geschätzt. Vor allem aber dürfen die TARMED-Positionen 39.3700 und 39.3710 nicht mit 24.0130 bzw. 24.0140	evidence was sought, and thus a logical implication of this stakeholder's view is that evidence for the use of IAGI in patients with activated OA is lacking. We acknowledge that, based on local clinical feedback, it does appear that the studied populations may have different disease profiles than Swiss practice. It is also noted that the THA included sub-group analyses that attempted to evaluate other possible effect-modifying variables, but the key concern raised of 'activated arthrosis' was not assessed due to the absence of data from this sub-population; the presence of joint effusion was evaluated where possible. 4. Expected per-patient costs associated with the delivery of a single injection were presented in the HTA. The narrow perspective/time horizon over which expected costs were considered may in part explain the specified narrow range. Insurer data were obtained to inform the estimated utilisation of the service. We acknowledge that the reliability of using data from one Swiss health insurer, extrapolated to the entire Swiss population based on their coverage rate, has limitations. Independent feedback from clinical reviewers reflects this uncertainty, with one reviewer suggesting the estimated number of patients treated with IAGI were reasonable, one suggesting they were not reasonable, and one suggesting they may be under-estimating patient numbers for knee OA by around 20%. In the absence of better data, we believe the data from the Swiss insurer still provides the most robust estimate for the size of the treated population, and have retained this in the base case for the budget impact analysis. To address this uncertainty, additional sensitivity analyses were done to account for +20% in knee OA, and ±10% for hip OA. 5. Section 7.5 of the HTA presents the data sources applied in the utilisation estimates. Data from one Swiss insurer, extrapolated to the total Swiss population, were used. To identify services specific to primary osteoarthritis of the knee or hip, ICD-10-GM codes were used in the insurer's data analysis. We acknowledge the limitations of relying on data from one insurer (see above). Feedback from clinical reviewers was sought to assess the validity of the estimates presented (see above). 6. Thank you for the feedback. The cost analysis considered a proportion of patients to be billed for TARMED position 39.3700 or 39.710 and the remaining proportion to be billed for position 24.0130 or 24.0140 (i.e. these were considered mutually exclusive options). Costs for TARMED positions 39.3700 or 39.710 were not cumulated with positions 24.0130 or 24.0140. However, costs for TARMED 00.1190 were erroneously accumulated with items 39.3700 or 39.3710 as an additional cost for patients modelled to receive local anaesthetic. This has been corrected in the final report. 7. Noted, thank you for the feedback.

	kumuliert werden! Auch eine Kumulation mit 00.1190 ist nicht zulässig. - Insgesamt bleibt die Unsicherheit des im HTA geschätzten Nutzens bei Schweizer Patienten somit hoch.	
5	1. The report is very extensive at 200 pages, there is little to complain about in terms of content appears to accurately reflect current evidence. It seems important to us to emphasize that with cortisone injections - and not paid much attention to this by those responsible at the BAG - it's not about curing, but about pain relief. Since a cure for Osteoarthritis does not exist until proven otherwise, combating the symptoms is the only way only therapeutic measure that we can offer to patients. Even if the evidence of the effect of cortisone infiltrations is low and the duration of the effect is not long-term, infiltrations remain important for both therapeutic and diagnostic aspects of osteoarthritis treatment. 2. Our regular experience is that right now acute inflammatory conditions such as activated osteoarthritis or Chondrocalcinosis these can be successfully used to treat pain and it is often only afterwards that patients are able to carry out more conservative measures such as physiotherapy successfully, they may also prevent temporary incapacity to work or allow for adequate timing of an operation for all involved by allowing postponement. Typically, steroid infiltrations are not used repetitively. There are however, settings such as old or multimorbid patients and Patients or inoperable patients in whom repetitive steroid infiltrations a valid, cost-effective, less invasive and works for patients represents strategy. It would be wrong if these patients were one would be deprived of such an option. 3. It is to be feared that steroid infiltration will be deleted from the catalog of services due to a lack of therapeutic alternatives, analogous to the practical one obsolete arthroscopy for osteoarthritis of the knee, leading to a further increase could lead to knee prosthesis implantations. Original German language response: Der Bericht ist mit 200 Seiten sehr umfangreich, inhaltlich ist wenig auszusetzen, er scheint die aktuelle Evidenz korrekt wiederzugeben. Uns scheint es wichtig zu betonen, dass es bei Kortisoninjektionen - und das scheint in der Zielsetzung der Behandlung von den Verantwortlichen des BAG wenig beachtet zu werden – nicht um eine Heilung, sondern um eine Schmerzlinderung geht. Da es eine Heilung der Arthrose bis zum Beweis des Gegenteils nicht gibt, ist die Symptombekämpfung die einzige therapeutische Massnahme, die wir den Patientinnen und Patienten anbieten können. Auch wenn die Evidenz der Wirkung von Cortison-Infiltrationen gering und die Wirkungsdauer nicht langfristig ist, bleiben Infiltrationen dennoch sowohl aus therapeutischen wie auch aus diagnostischen Gründen wichtig für die Arthrosebehandlung. Unsere regelmässigen Erfahrungen sind, dass gerade in akuten Entzündungszuständen wie z.B. einer aktivierten Arthrose oder einer Chondrokalzinose diese erfolgreich zur Schmerzbehandlung eingesetzt werden können und es den Patientinnen und Patienten oft erst danach möglich ist, weitere konservative Massnahmen wie zum Beispiel eine Physiotherapie überhaupt erfolgreich durchführen zu können, sie verhindern unter Umständen auch eine vorübergehende Arbeitsunfähigkeit oder lassen eine für	1. Noted, thank you for the feedback. This is potentially a limitation to the HTA since patients enrolled in the RCTs were not specifically enrolled based on presenting with activated arthrosis. The evidence base for activated arthrosis being more responsive to IAGI is, however, unclear. 2. Noted, thank you for the feedback. 3. Noted, thank you for the feedback.

	alle Betroffenen adäquates Timing einer Operation zu, indem der Zeitpunkt hinausgeschoben werden kann. Üblicherweise werden Steroidinfiltrationen nicht repetitiv eingesetzt. Es gibt allerdings Settings wie zum Beispiel bei alten oder multimorbiden Patientinnen und Patienten oder bei Inoperabilität, in denen repetitive Steroidinfiltrationen eine valide, kostengünstige, wenig invasive und für die Patienten funktionierende Strategie darstellt. Es wäre falsch, wenn diese Patientinnen und Patienten einer solchen Option beraubt würden. Es steht zu befürchten, dass eine Streichung der Steroidinfiltration aus dem Leistungskatalog mangels therapeutischen Alternativen, analog der praktisch obsoleten Arthroskopie beim Arthroseknie, zu einer weiteren Zunahme der Knieprothesen-Implantationen führen könnte.	