Health Technology Assessment (HTA)

Stakeholder Feedback on the HTA report on Calcitonin Gene-Related Peptide Antagonists for the Prevention of Migraine

Contents

1 Preface

This document details the authors' responses to stakeholder feedback on the HTA report on *calcitonin gene-related peptide antagonists for the prevention of migraine.*

The stakeholder feedback and corresponding author responses are detailed in tables. Responses provided in the tables are listed by stakeholder, in alphabetical order.

Comments that have been translated from German into English are provided in blue font.

Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response.

The following stakeholders were invited to submit feedback:

- ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana
- BSV - Bundesamt für Sozialversicherung, Invalidenversicherung
- curafutura - Die innovativen Krankenversicherer
- DVSP - Dachverband Schweizerischer Patientenstellen
- Eli Lilly (Suisse) SA
- FMH - Verbindung der Schweizer Ärztinnen und Ärzte
- FRC - Fédération romande des consommateurs
- GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren
- GSASA - Schweizerischer Verein der Amts- und Spitalapotheker
- H+ - Die Spitäler der Schweiz
- Intergenerika - Swiss Generics and Biosimilars
- Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz
- Konsumentenforum
- Lundbeck (Schweiz)
- Migraine Action
- MTK - Medizinaltarif-Kommission
- Novartis Pharma Schweiz AG
- pharmaSuisse - Schweizerischer Apothekerverband
- PUE - Preisüberwachung
- SAMW - Schweizerische Akademie der Medizinischen Wissenschaften
- santésuisse - Die Schweizer Krankenversicherer
- SAPhW - Schweizerische Akademie der Pharmazeutischen Wissenschaften
- sQmh - Schweizerische Gesellschaft für Qualitätsmanagement im Gesundheitswesen
- SGAIM Schweizerische Gesellschaft für Allgemeine Innere Medizin
- SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte
- SKG - Schweizerische Kopfwehgesellschaft
- SKS - Stiftung für Konsumentenschutz
- SNG - Schweizerische Neurologische Gesellschaft
- SPO - Patientenschutz
- SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen
- Teva Pharma
- Verein Migräneforschung Schweiz
- VIPS - Vereinigung Pharmafirmen in der Schweiz

Feedback was received from the following stakeholders:

- Eli Lilly (Suisse) SA
- Interpharma (IPH)
- Lundbeck (Schweiz)
- Migraine Action
- Santésuisse
- Schweizerische Kopfwehgesellschaft (SKG)
- Schweizerische Neurologische Gesellschaft (SNG)
- Teva Pharma AG

2 General comment on the HTA report

Stakeholder / Comment number	Author Response
Eli Lilly (Suisse) SA 1. Der vorliegende HTA-Bericht befasst sich mit innovativen Arzneimitteln zur Migräneprophylaxe. Da die Forschung in diesem Gebiet rasch voranschreitet, können Literatur-Recherchen innerhalb kurzer Zeit veraltet sein. Der Bericht basiert überwiegend auf Daten aus dem Zulassungsverfahren. Die Berücksichtigung von Real-World-Daten wäre für eine fundierte Auswertung des Nutzen-/Risiko-/Kosten-Verhältnisses der anti-CGRP-Therapie wünschenswert gewesen. This HTA report deals with innovative drugs for migraine prophylaxis. As research in this area advances rapidly, literature searches can become outdated within a short period of time. The report is mainly based on data from the approval process. Consideration of real-world data would have been desirable for a well-founded evaluation of the benefit/risk/cost ratio of anti-CGRP therapy. 2. Der vorliegende HTA-Bericht zeigt Inkonsistenzen zwischen den klinischen Studien, insbesondere in der eingeschlossenen Population von Patienten mit vorausgegangenem Versagen von ≥ 2 Therapien. Da die Unterschiede bei den Patientenpopulationen bzw. beim Versagen vorheriger Therapien in den klinischen Studien einen Vergleich innerhalb der Klasse kaum zulassen, wäre ein Vergleich der anti-CGRP-Therapie zur Standardbehandlung hilfreich gewesen. The present HTA report shows inconsistencies between the clinical studies, especially in the included population of patients with prior failure of ≥ 2 therapies. Since the differences in the patient populations and the failure of previous therapies in the clinical studies hardly allow a comparison within the class, a comparison of the anti-CGRP therapy to the standard treatment would have been helpful.	1. We acknowledge the speed at which literature is developing in this area, which is why an updated search was conducted shortly before finalising the draft report. It was agreed with the FOPH, during the protocol phase, that observational studies would only be sourced in the absence of RCT data. Observational data was screened for literature on whether switching from one CGRP antagonist to another is effective/efficacious in those who previously experienced inadequate treatment effects using a different CGRP antagonist, due to an absence of RCT data addressing this question, although no relevant evidence was identified. 2. It is noted that there are inconsistencies in the literature. Only direct comparative evidence was considered for inclusion in this HTA, and no evidence was available to compare the CGRP antagonists to the current standard of care.
Interpharma (IPH) 3. Wir bedanken uns für die Zustellung des HTA-Berichts «Calcitonin gene-related peptide antagonists for the prevention of migraine». Mit diesem Schreiben nehmen wir fristgerecht die Gelegenheit zur Stellungnahme zum HTA-Bericht wahr. Als Verband der innovativen Arzneimittelhersteller konzentriert sich Interpharma in dieser Stellungnahme auf übergeordnete Aspekte und geht nicht im Detail auf behandlungsspezifische Aspekte ein. Der vorliegende HTA-Bericht befasst sich mit innovativen Medikamenten zur Migräneprophylaxe. Diese Medikamente stehen aufgrund der Limitatio bereits heute nur Patientinnen und Patienten zur Verfügung, die auf andere prophylaktische Therapien nicht angesprochen haben. Somit sind diese Medikamente für die Patientinnen und Patienten in der Schweiz als wichtige Therapieoption von grosser Relevanz. Die Forschung im Bereich	3. We acknowledge the speed at which literature is developing in this area, which is why an updated search was conducted shortly before finalising the draft report. It was agreed with the FOPH, during the protocol phase, that observational studies would only be sourced in the absence of RCT data. Observational data was screened for literature on whether switching from one CGRP antagonist to another is effective/efficacious in those who previously experienced inadequate treatment effects using a different CGRP antagonist, due to an absence of RCT data addressing this question, although no relevant evidence was identified.

Stakeholder / Comment number	Author Response
der anti-CGRP Therapie schreitet zudem rasch voran und Literatur Recherchen sind innerhalb kurzer Zeit veraltet. Der HTA-Bericht basiert nun mehrheitlich auf Daten, die bereits für den Zulassungsprozess herangezogen wurden. Der Einschluss von Real-World Daten hätte in diesem Zusammenhang zu einer fundierteren Analyse des Nutzen-/Risiko-/Kosten-Verhältnisses der anti-CGRP Therapie beigetragen. Thank you for submitting the HTA report "Calcitonin gene-related peptide antagonists for the prevention of migraine". With this letter we take the timely opportunity to comment on the HTA report. As an association of innovative drug manufacturers. In this statement, Interpharma focuses on overarching aspects and does not go into detail on treatment-specific aspects. This HTA report deals with innovative drugs for migraine prophylaxis. Due to the limitations, these drugs are already only available to patients who have not responded to other prophylactic therapies. These drugs are therefore of great relevance for patients in Switzerland as an important therapy option. Research in the field of anti-CGRP therapy is also progressing rapidly and literature searches are outdated within a short time. The HTA report is now mostly based on data that was already used for the approval process. In this context, the inclusion of real-world data would have contributed to a more informed analysis of the benefit/risk/cost ratio of anti-CGRP therapy.	
Lundbeck (Schweiz) 4. Eptinezumab (Vyepti) ist ein CGRP-Antagonist (aCGRP), wie die drei anderen von Swissmedic zugelassen und vom BAG SL-gelistet. Damit sind Wirksamkeit, Sicherheit und Verträglichkeit bereits wiederholt bestätigt; die Wirtschaftlichkeit ist mit der SL-Aufnahme sichergestellt. Eptinezumab (Vyepti) is a CGRP antagonist (aCGRP), like the three others, approved by Swissmedic and SL-listed by the FOPH. This means that effectiveness, safety and tolerability have already been repeatedly confirmed; the economy is ensured with the SL mount. 5. Patienten dürfen gemäss Limitation nur mit aCGRP therapiert werden, wenn konventionelle Prophylaktika nicht mehr verwendet werden können. Damit sind aCGRP wie z.B. Vyepti für diese Patienten die einzige pharmakologische Therapieoption und Standard of Care. According to the limitation, patients may only be treated with aCGRP if conventional prophylactics can no longer be used. This makes aCGRP such as Vyepti the only pharmacological therapy option and standard of care for these patients. 6. Die im HTA berücksichtigten Daten für Vyepti entsprechen nicht immer der aktuell verfügbaren Evidenz. Von Bedeutung ist daher der Einbezug der RCT DELIVER, die in der ergänzenden Recherche identifiziert wurde. Diese Studie ist insbesondere deshalb von	4. Thank you for this feedback, it is noted but no change to the report is needed. 5. Thank you for this feedback, it is noted but no change to the report is needed. 6. Thank you for this feedback, it is noted but no change to the report is needed. As you correctly point out, the DELIVER trial was included in the report in the postface chapter for both the clinical and economic evaluations.

Stakeholder / Comment number	Author Response
hoher Relevanz, da die Patientenpopulation den Vorgaben der Limitation entspricht und damit optimale Ableitungen für den Schweizer Versorgungsalltag ermöglicht. The data for Vyepti considered in the HTA do not always correspond to the currently available evidence. It is therefore important to include the RCT DELIVER, which was identified in the supplementary research. This study is particularly relevant because the patient population corresponds to the requirements of the limitation and thus enables optimal derivations for everyday Swiss care.	
Migraine Action 7. The submitted document is well-structured and supported by solid research on migraine and its management although it seems that the report is somehow artificial, the real life impact of this long-term neurological disorder and its resulting costs seem to be under-represented: a. Direct cost resulting from comorbidities (e.g. depression and anxiety and…) if migraine is not adequately taken care of (e.g. ineffectiveness of chosen treatments, intolerance or interaction with other treatments, low adherence…). b. CGRP's additional benefits e.g. maintained efficacy on reducing depression in patients are not mentioned e.g. Fremanezumab efficacy vs placebo (double blind) on MMD maintained for 24 weeks and maintained efficacy on reducing depression in patients (Lipton R, Barbanti P, Ramirez Campos V et al. Efficacy of fremanezumab in reducing depression in patients with migraine and major depressive disorder: results of the UNITE study. Headache 2023; 63 Suppl. 1:133 (IO-05)	7. a. The standard methodological approach for costing interventions in FOPH HTA projects is to consider direct medical costs related to the intervention, as well as direct medical costs associated with adverse events that result from the application of the intervention. The effectiveness of the treatments is considered in the economic analysis in relation to quality-adjusted life years experienced by patients that receive each intervention. Treatment adherence was listed in the PICO criteria; however, no evidence was identified that looked at this outcome from the included RCTs. A discontinuation rate that captured patient preference, adverse events and response was included in economic modelling. No changes to the report needed. b. Thank you for the feedback, it is noted. The cited article is a conference abstract, which is not eligible for inclusion in the HTA per the predefined inclusion criteria. Publication of the full results from the trial may contribute to the re-evaluation of CGRP antagonists in future.
Santésuisse 8. The HTA report is detailed and well structured. It shows the data found in a good and comprehensive way, but also points out gaps.	8. Thank you for this feedback.
Schweizerische Kopfwehgesellschaft (SKG) 9. The authors of the HTA-report present a carefully conducted extensive analysis based on available data. As they state, "generalisability to the Swiss context is relatively uncertain" and it remains opaque what they refer to as an input from "Swiss clinical expert opinion". 10. The modelling relies on many unvalidated and in part, wrong assumptions, hence compromising the conclusions that can be drawn from the analysis.	9. "Swiss clinical expert opinion" refers to feedback received from a panel of independent clinical experts that were employed by the FOPH to review the draft protocol and HTA report. The independent experts remain anonymous to the HTA authors throughout the entire review process. 10. Specific comments relating to the limitations in the economic section have been responded to below, in Section ***5. Comments on health economic evaluation and budget impact analysis***.
Schweizerische Neurologische Gesellschaft (SNG)	11. Thank you for this feedback, it is noted but no change to the report is needed.

Stakeholder / Comment number	Author Response
11. Dieser sehr umfangreiche und mit viel Aufwand erstellte Bericht präsentiert eine Modellrechnung, die auf Annahmen beruht, von denen die Autoren selber zugeben, dass ihre Anwendbarkeit auf die Schweizer Verhältnisse unsicher ist. This very extensive and laboriously prepared report presents a model calculation based on assumptions which the authors themselves admit are uncertain as to their applicability to Swiss conditions. 12. Zudem sind einige dieser Annahmen unbelegt oder falsch. Durch diese Mängel ist die Analyse leider kaum für die Einschätzung der Kosteneffektivität noch die der Gesamtkosten verwertbar. In addition, some of these assumptions are unsubstantiated or wrong. Unfortunately, due to these shortcomings, the analysis is hardly usable for assessing the cost-effectiveness or the overall costs.	12. Specific comments relating to the limitations in the economic section have been responded to below, in Section ***5. Comments on health economic evaluation and budget impact analysis***.
Teva Pharma AG 13. This HTA suggests that anti-CGRPs are more cost-effective for CM patients compared to EM patients. However, in Switzerland, strict reimbursement criteria limit access to anti-CGRPs to high-frequency EM (HFEM) patients (> 8 migraine days). Therefore, we believe that the chosen population for cost-effectiveness calculations for EM is incorrect and needs adjustment. 14. Additionally, this HTA shows that prophylaxis with anti-CGRPs results in significantly fewer MMDs, more patients with a response rate of ≥50%, and improvements in MSQ without significant adverse effects, unlike conventional SoC treatments. As a result, anti-CGRPs should be considered a SoC/comparator rather than oral preventive options for the treatment of failed population. 15. Although there were sufficient RCTs to answer the key questions in this HTA, we believe that RWE would have been valuable, especially for assessing reimbursement conditions (switch-data), long-term efficacy and safety.	13. Thank you for this feedback. The HTA presents cost-effectiveness analysis for EM and CM patients. Based on mid-ranges in the clinical evidence, the EM models assume base migraine days of 9 and CM models 18 migraine days per month. These migraine day assumptions are aligned with Swiss reimbursement criteria. The Spezialitätenliste[2] (as highlighted in Appendix A of the HTA report indicates that "Episodic migraine patients have to experience migraines with attacks that last at least 4 hours on at least 8 days per month" for CGRP antagonists to be prescribed. No change to the report is needed. 14. Thank you for this feedback, it is noted. No changes to the report are needed. 15. It was agreed with the FOPH, during the protocol phase, that observational studies would only be sourced in the absence of RCT data. Observational data was screened for literature on whether switching from one CGRP antagonist to another is effective/efficacious in those who previously experienced inadequate treatment effects using a different CGRP antagonist, due to an absence of RCT data addressing this question, although no relevant evidence was identified.

3 Comments on efficacy, effectiveness and safety

Stakeholder / Comment	Author Response
Eli Lilly (Suisse) SA 1. Zur scheinbar grösseren Kosteneffizienz von Erenumab (ERE) vs. Galcanezumab (GALCA) kann geführt haben: - Die GALCA-Studien erlaubten 3 und 4 vorherige Therapien, die ERE-Studien ein Versagen von bis zu 2 vorherigen Therapien. Dies kann zu einem Unterschied in der Effektstärke führen, und möglicherweise zur Schlussfolgerung, dass ERE kosteneffektiver als GALCA sei. - In den ERE-Studien wies ein viel kleinerer Teil der Gesamtpopulation ein Versagen von ≥ 2 vorherigen Therapien auf. Je chronischer der Patient, desto schwieriger ist die Behandlung. Die ERE-Studien schlossen zwar insgesamt mehr Patienten ein, jedoch weniger Patienten mit Versagen von ≥ 2 vorherigen Therapien. - Die HER-MES Studie zu ERE umfasste nur aktive Therapiearme. Beim Vergleich der Veränderung von Migräne-Kopfschmerz-Tagen oder monatlichen Migräne-Tagen gegenüber dem Studienbeginn ist zu erwarten, dass das Ergebnis in dieser Studie für ERE besser ausfällt als bei einem Vergleich in einer placebokontrollierten Studie. The apparently greater cost-effectiveness of erenumab (ERE) vs. galcanezumab (GALCA) may have led to: - The GALCA studies allowed 3 and 4 prior therapies, the ERE studies a failure of up to 2 prior therapies. This may lead to a difference in effect size, possibly leading to the conclusion that ERE is more cost-effective than GALCA. - In the ERE studies, a much smaller proportion of the overall population had failures of ≥ 2 prior therapies. The more chronic the patient, the more difficult the treatment. The ERE studies enrolled more patients overall, but fewer patients with failure of ≥ 2 prior therapies. - The HER-MES study on ERE included only active treatment arms. When comparing change from baseline in migraine headache days or monthly migraine days, the outcome in this study for ERE is expected to be better than a comparison in a placebo-controlled study.	1. Thanks for the feedback. These uncertainties will be included in the report.
Interpharma (IPH) No comment provided.	N/A

Stakeholder / Comment	Author Response
Lundbeck (Schweiz) Folgende Aussagen im Dossier sollten korrigiert bzw. entsprechende Daten dargestellt werden. The following statements in the dossier should be corrected or corresponding data presented. 2. Aussage: “The duration of treatment ranged from 3–9 months”. In PROMISE-1 wurden Patienten mit bis zu 4 Dosierungen Eptinezumab behandelt, was einer Behandlungsdauer von 48 Wochen entspricht (nicht 9 Monaten od. 36 Wochen). 1st statement: “The duration of treatment ranged from 3–9 months”. In PROMISE-1, patients were treated with up to 4 doses of eptinezumab, which corresponds to a treatment duration of 48 weeks (not 9 months or 36 weeks). 3. Aussage “MSQ, (...) mortality, AEs, TRAEs (...) were not reported for eptinezumab.” Zu diesen Endpunkten liegen Daten vor: MSQ: doi:10.1111/ene.15670; Mortalität (keine Fälle), AEs (in Eptinezumab Studien: TEAEs) und TRAEs sind in allen hier aufgeführten Studien publiziert. Statement “MSQ, (...) mortality, AEs, TRAEs (...) were not reported for eptinezumab.” Data are available for these endpoints: MSQ: doi:10.1111/ene.15670; Mortality (no cases), AEs (in eptinezumab studies: TEAEs) and TRAEs are published in all studies listed here. 4. Für die Studie PROMISE-1 wird ein hohes Bias-Risiko postuliert: “Outcomes were not fully reported at the pre-specified timepoints and the timepoints reported may have been selected based on the results.” Diese Aussage ist nicht nachvollziehbar: In der Erstveröffentlichung von PROMISE-1 wurde der primäre Endpunkt sowie alle prä-spezifizierten "key" sekundären Endpunkte publiziert. A high risk of bias is postulated for the PROMISE-1 study: "Outcomes were not fully reported at the pre-specified timepoints and the timepoints reported may have been selected based on the results." This statement is not comprehensible: In the first publication of PROMISE-1, the primary endpoint and all pre-specified "key" secondary endpoints were published.	2. Per Ashina 2020 (ref 79 in the report), “*Patients received up to four treatments of eptinezumab or placebo (administered IV day 0, week 12, week 24, and week 36)”*. Duration of treatment and duration of follow-up are reported separately in Table 4. No change required. 3. These statements are based on the results of the original searches. The results from the DELIVER trial (cited here) are included in the postface to the clinical chapter, which documents results for MSQ, TRAWs, AEs, and AEs leading to discontinuation. No change required. 4. There are partial analyses reported for some outcomes. For example, the SF-36 is (partially) reported at 12 weeks in the NCT record and at 4, 24 and 36 weeks in the publication (also partial). There are also different outcomes reported in different publications, for example, the publication reports ORs for binary outcomes, while the NCT record reports differences between groups. Risk of bias is evaluated in relation to the list of outcomes relevant to the current HTA and are not based on the key endpoints of the trial. No change required.

Stakeholder / Comment	Author Response
Migraine Action 5. CGRP's have sustained benefits in previous treatment failures. Marked and sustained reductions in monthly migraine days (MMDs) and improvements in migraine severity and burden for up to 18 months have been reported e.g. from the DELIVER study in patients with migraine who had two to four documented preventive treatment failures. CGRP's have good side effect profile and low contraindication profile "The risk of vascular adverse events among patients with migraine treated with erenumab was similar to that with other migraine preventive migraine medications, including other CGRP mAbs and onabotulinumtoxin A. (Dodick D, Ailani J, Oh S et al. Effect of erenumab versus migraine preventive medications on cardiovascular and cerebrovascular outcomes. Headache 2023; 63 Suppl. 1: 51 (IO-04)	5. Thank you for this feedback, it is noted. The provided citation is a conference abstract for retrospective observational study. Per the predefined inclusion criteria, conference abstracts were not eligible for inclusion in the HTA. No changes to the report are needed.
Santésuisse 6. Although CGRP antagonists have only been on the market for a few years, there are already various studies that examine their efficacy in comparison to placebo. Nevertheless, there are important gaps in knowledge, which are addressed in chapter 10 of the HTA. In addition to the poorly investigated safety issues ("not well reported adverse events"), these include in particular the duration of the studies (duration of treatment mostly in between 8 weeks and 6 months). As also stated in the HTA, it thus remains completely unknown what the long-term efficacy and above all the long-term safety look like. 7. We very much welcome the fact that a new, brief literature search was carried out shortly before the report was submitted. Nevertheless, the same important questions remain largely unanswered.	6. Thank you for this feedback, it is noted. No changes to the report are needed. 7. Thank you for this feedback, it is noted. No changes to the report are needed.
Schweizerische Kopfwehgesellschaft (SKG) 8. The HTA- report confirms that CGRP antagonisation is highly effective and safe as a preventive treatment of episodic and chronic migraine. Unfortunately, it does not point out that adverse effects are significantly lower than in prior SOC treatments.	8. Thank you for this feedback, it is noted. The HTA summarises the available evidence from RCTs on the safety profile of CGRP antagonists. It is also acknowledged in the report that there are limitations in the reported safety data. No changes to the report are needed.

Stakeholder / Comment	Author Response
Schweizerische Neurologische Gesellschaft (SNG) 9. Wirksamkeit und Sicherheit sind aus einer grossen Zahl qualitativ hochwertiger Studien wohl bekannt, und der vorliegende Bericht bestätigt dies. Es kann von unserer Seite nicht nachvollzogen werden, warum die Autoren von Unzulänglichkeiten in der Darstellung unerwünschter Wirkungen ausgehen. Diese sind im Gegenteil sehr gut bekannt und repliziert, aber insgesamt erfreulich selten, was einen wesentlichen Vorteil gegenüber klassischen Behandlungsoptionen darstellt. Efficacy and safety are well established from a large number of high quality studies and this report confirms this. From our side, it cannot be understood why the authors assume inadequacies in the description of undesirable effects. On the contrary, these are very well known and replicated, but overall pleasingly rare, which represents a significant advantage over classic treatment options.	9. Thank you for this feedback. The conclusions around relative safety are based on the reported RCT data, which has limitations as noted in the report. No changes to the report are needed.
Teva Pharma AG 10. The latest guidelines (EHF + DGN 2022) have not been considered in this HTA, despite their importance in providing updated efficacy criteria for anti-CGRP prophylaxis. These guidelines can also play a crucial role in determining reimbursement criteria. 11. According to this HTA, galcanezumab is classified as having stronger evidence from RCTs compared to fremanezumab, but both anti-CGRPs have seven available RCT studies with similar patient numbers. 12. Although the omission of RWE studies in this HTA is criticized for lacking long-term data, it is important to note that all included studies fulfilled the requirements for clinical studies, including documentation of AEs. However, the reporting of AEs in the included studies is deemed inadequate. The inclusion of RWE would confirm the favorable safety profile of anti-CGRPs but was not considered in this HTA.	10. Guidelines are not considered as evidence in the clinical evaluation of HTA reports, but are covered in the section ***9. Additional Issues,*** and further detailed in ***Appendix N***. Guidelines and position statements available during the production of the report were included. The original European Headache Federation (EHF) guideline from 2019 is already summarised in ***Appendix N***. The 2021 update has been added to ***Appendix N*** also. 11. Please note that no direct comparisons are made in the HTA between different CGRP antagonists. Participant numbers in trials are not an indicator of treatment effectiveness. No changes to the report are needed. 12. Thank you for this feedback. It is noted. No changes will be made to the HTA report at this stage as expanding the evidence base to include NRSIs is outside of scope for this HTA.

4 Comments on health economic evaluation and budget impact analysis

Stakeholder / Comment	Author Response
Eli Lilly (Suisse) SA 1. Es bleibt unklar, wie die bestehenden Preismodelle bei der Kosteneffektivitätsanalyse berücksichtigt werden. Der in der Berechnung angenommene Rabatt von lediglich 3% entspricht nicht der Realität. Wir würden uns klare Richtlinien zum Umgang mit vertraulichen Preismodellen im Rahmen von HTAs wünschen, um eine realistische Kosteneffektivitätsanalyse zu ermöglichen, unter Gewährleistung der Vertraulichkeit. It remains unclear how the existing pricing models are taken into account in the cost-effectiveness analysis. The discount of only 3% assumed in the calculation does not correspond to reality. We would like clear guidelines on how to deal with confidential pricing models in HTAs to enable a realistic cost-effectiveness analysis while ensuring confidentiality. 2. Laut HTA-Bericht sind 72 - 98% der durch Migräne verursachten Kosten auf indirekte Kosten zurückzuführen (z. B. Arbeits- und Produktivitätsausfall). Dennoch werden die mit Migräne verbundenen indirekten Kosten im HTA-Bericht nicht berücksichtigt. Ohne Einschluss der indirekten Kosten in die Analyse, bleiben die gesamtgesellschaftlichen Auswirkungen unklar. According to the HTA report, 72-98% of the costs caused by migraines are due to indirect costs (e.g. lost work and productivity). However, the indirect costs associated with migraine are not included in the HTA report. Without including the indirect costs in the analysis, the societal effects remain unclear. 3. Die derzeit geltenden Beschränkungen für die Erstattung von anti-CGRP-Therapien sind sehr streng und umfassen Stoppregeln (Fortsetzung nach 3, 6 und 9 Monaten), die in der Budgetauswirkungsanalyse hätten berücksichtigt werden können. The current restrictions on the reimbursement of anti-CGRP therapies are very strict and include stopping rules (3, 6 and 9 month continuation) that could have been considered in the budget impact analysis	1. There appears to be confusion about the inclusion of a 3% discount rate. This rate is applied to future costs and benefits in the cost-effectiveness model to covert these values into a present value. The discount is not applied to pricing. Only the official prices sourced from the Spezialitätenliste for each CGRP antagonist were considered as cost inputs for the economic model. No change is needed in the report. A statement about how discount rates are applied will be included. 2. As per FOPH guidance, no indirect costs are included in the economic evaluation. No change is included in the report. 3. Thank you for the feedback. There is currently no readily available data about the proportions of patients stopping at 3, 6 and 9 months in Switzerland. The response rate from key clinical trials has been included in budget impact scenarios. No change is included in the report.

Stakeholder / Comment	Author Response
Interpharma (IPH) Gerne möchten wir Sie auf einige weitere kritische Punkte aufmerksam machen: We would like to draw your attention to a few other critical points: 4. Im HTA-Bericht wird beschrieben, dass 72-98% der durch Migräne verursachten Kosten auf indirekte Kosten zurückzuführen sind (z.B. Arbeits- und Produktivitätsausfall). Dennoch werden die mit Migräne verbundenen indirekten Kosten im HTA-Bericht nicht berücksichtigt. Ohne Einschluss der indirekten Kosten in die Analyse, wird der Anspruch der gesamtgesellschaftlichen Betrachtung nicht erfüllt. The HTA report describes that 72-98% of the costs caused by migraines are due to indirect costs (e.g. lost work and productivity). However, the indirect costs associated with migraine are not included in the HTA report. If the indirect costs are not included in the analysis, the requirement of considering society as a whole will not be met. 5. Wir weisen nochmals mit Nachdruck darauf hin, dass in der Schweiz für die Definition und Anwendung von Kosten-Grenzwerten zur Kosten-Nutzen Bewertung im Rahmen von HTA-Protokollen und Berichten keine Grundlage besteht (vgl. Schreiben vom 12. August 2022). We would like to emphasize once again that in Switzerland there is no basis for the definition and application of cost limit values for cost-benefit assessments within the framework of HTA protocols and reports (see letter of August 12, 2022). 6. Die im vorliegenden HTA angewandten Berechnungen sind nicht ausreichend transparent, um nachvollziehbar zu sein. Insbesondere bleibt dabei unklar, wie bestehende Preismodelle im Rahmen der Kosteneffektivitätsanalyse berücksichtigt werden. Der in der Berechnung angenommene Rabatt von lediglich 3% entspricht nicht der Realität und stellt den Nutzen der Analyse in Frage. Interpharma sieht es als Aufgabe des BAGs klare Richtlinien zum Umgang mit vertraulichen Preismodellen im Rahmen von HTAs festzulegen, um eine realistische Kosteneffektivitätsanalyse zu ermöglichen. Die strenge Vertraulichkeit muss dabei jederzeit gewährleistet bleiben. The calculations used in this HTA are not sufficiently transparent to be comprehensible. In particular, it remains unclear how existing price models are taken into account in the cost-effectiveness analysis. The discount of only 3% assumed in the calculation does not correspond to reality and calls into question the usefulness of the analysis. Interpharma sees it as the BAG's task to define clear guidelines for dealing with confidential price models within the framework of HTAs in order to enable a realistic cost-effectiveness analysis. Strict confidentiality must be guaranteed at all times.	4. As above, indirect costs are not included based on FOPH guidelines. 5. Thank you for the feedback. No cost limit values or willingness to pay thresholds are explicitly stated in the economic evaluation. No changes will be made to the report. 6. As above, discount rates are applied to future costs and benefits, and not pricing. Only the official prices sourced from the Spezialitätenliste for each CGRP antagonist were considered as cost inputs for the economic model. No change is needed in the report.

Stakeholder / Comment	Author Response
Lundbeck (Schweiz) 7. Mit der SL-Aufnahme von Vyepti durch das BAG sowie der bereits erfolgten Überprüfung ist sichergestellt, dass der jeweils aktuelle Preis wirtschaftlich ist; der aktuelle Preis von Vyepti ist jedoch im HTA nicht herangezogen. With the SL acceptance of Vyepti by the BAG and the review that has already taken place, it is ensured that the current price is economical; however, the current price of Vyepti is not included in the HTA. 8. Die Kostenberechnungen im HTA basieren auf veralteten Kostendaten und sind regelhaft methodisch nicht nachvollziehbar. Die Berechnungsmethodiken sollten nachvollziehbar dargestellt werden und den Rahmenbedingungen des Schweizer Gesundheitssystems entsprechen, bei dem es z.B. keinen „willingness-to-pay threshold“ gibt. The cost calculations in the HTA are based on outdated cost data and are generally methodologically incomprehensible. The calculation methods should be presented in a comprehensible manner and correspond to the framework conditions of the Swiss healthcare system, in which there is no "willingness-to-pay threshold", for example. 9. Von Bedeutung ist ebenfalls der Einbezug der RCT DELIVER wegen deren guter Übertragbarkeit auf den Schweizer Versorgungsalltag (s.a. 1. oben). The inclusion of the RCT DELIVER is also important because of its good transferability to everyday Swiss care (see also 1. above). 10. Der veraltete Status der in Tab. 2 (HTA-Report) dargestellten Erstattungsbedingungen in Europa sollte aktualisiert werden. The outdated status of the reimbursement conditions in Europe shown in Table 2 (HTA report) should be updated. 11. In der prognostischen Budget Impact Analyse wird eine Zunahme behandelter Patienten von bis zu 50% bei identischen Preisen angenommen. Der Sinn solch hochspekulativer Annahmen ist unklar. In the prognostic budget impact analysis, an increase in treated patients of up to 50% is assumed with identical prices. The point of such highly speculative assumptions is unclear.	7. Thank you for the feedback. The prices available at the time of drafting the report have been included in the economic model. These prices may have been subsequently revised after the draft report was finalised. The lower price (i.e. CHF 1396) will not significantly change the ICER. 8. Thank you for the feedback. Unit costs have been calculated using Swiss data, where possible. No willingness-to-pay threshold has been included. No changes are to be included in the report. 9. The DELIVER RCT trial results were included in the economic modelling post-subscript analysis. No changes are included in the report. 10. Reimbursement conditions in Europe have been updated to 7 August 2023, based on publicly available tariff databases. 11. Thank you for the feedback. The potential for uptake in Switzerland is unclear. A number of scenarios were presented to gauge potential cost implications. No speculation about the possibility of such scenarios becoming evident in the future have been provided in the report. No changes to the report are included.

Stakeholder / Comment	Author Response
Migraine Action 12. In the evaluation of costs it seem be not taken notice that CGRP's are not straight away offered to ALL migraine patients but to a SELECTED group of patients, especially to patients with migraine who had two or more documented preventive treatment failures and with a minimal request of headache days per months. 13. Migraine often coexists with other medical conditions,which can significantly impact the overall healthcare costs. Several studies have reported that rates of comorbidities increase by headache day frequency among people with migraine comparing people with EM and CM and/or stratifying by frequency (Migraine progression: a systematic review. Headache 59:306–338. and Lampl C, Andrée C, (2016) Headache, depression and anxiety: J Headache Pain 17:59.) 14. As medication / treatment only work if taken, the preventon therapy adherence coefficient is important for the costs of comorbidities.	12. Thank you for the feedback. The proportions of EM and CM patients in Switzerland who are utilising preventive treatment and have failed two treatments is unclear. It is likely that a greater proportion of CM patients would use preventive treatment compared to EM patients, however, the magnitude of this possible difference in Switzerland is not clear. The proportion of Swiss EM patients who are eligible for CGRP's (>8 migraine days per month) is also uncertain. A range of uptake scenarios are provided to accommodate these uncertainties. They are applied to all migraine patients. 13. The use of direct medical costs is a standard methodology for FOPH HTA projects. No changes required. 14. There is no readily available data about adherence and consequent treatment effectiveness in Switzerland. Economic modelling includes assumptions about response and longer-term discontinuation from clinical trials. No changes required.
Santésuisse 15. The health economic evaluation and budget impact analysis is clearly and comprehensibly structured. The results are plausible.The present evaluation is a robust basis for decision-making on possible further restrictions of drug therapy with CGRP antagonists.	15. Thank you for the feedback, no changes required.
Schweizerische Kopfwehgesellschaft (SKG) 16. The analysis is based purely on direct costs which is inappropriate and introduces a negative bias (see point 4). 17. The extraction of QALYs seems to be driven by migraine days, hence ignoring non-headache related disease burden that is known to be considerable as well. 18. Costs beyond preventive medication are lower for any successful preventive treatment (less rescue medication and less visits to GP, neurologist and ER) than for unsuccessful treatment whereas the analysis seems to factor in additional costs. 19. As reimbursement in Switzerland requires at least 8 MMDs in baseline, the estimation for episodic migraine is wrong in numbers of patients (too many) and cost-effectiveness (too low). 20. Regarding budget impact, it is obvious from all that is well known about migraine care that uptake scenarios of 50 or even 25% are entirely unrealistic within the Swiss healthcare system.	16. The use of direct medical costs is a standard methodology for FOPH HTA projects. No changes required. 17. Thank you for the feedback. QALYs are driven by migraine days, and it is noted that non-headache related disease burden may impact patient quality of life. Data limitations precluded inclusion of these dimensions of disease burden. Sensitivity analyses have been provided in the report to account for quality-of-life uncertainty. No changes required. 18. Thank you for the feedback. Migraine management costs for the intervention and comparator arms of the economic models are calculated using numbers of migraine days. Correspondingly, GP, neurologist and ER costs are lower for more effective treatment. No changes required. 19. As above, base migraine days for CM and EM economic models (9 and 18) are in line with Swiss reimbursement criteria. The budget impact model assumes the same preventive treatment use and failed therapy for all patients due to a lack of Swiss data. 20. As above, the potential for uptake in Switzerland is unclear. A number of scenarios were presented to gauge potential cost implications.

Stakeholder / Comment	Author Response
Schweizerische Neurologische Gesellschaft (SNG) 21. Es ist nicht nachvollziehbar, warum für anti-CGRP Behandlung Zusatzkosten im Vergleich mit Standardtherapien unterstellt werden. Das Gegenteil ist wahr: jegliche erfolgreiche Migräneprophylaxe reduziert Kosten für Akutmedikamente sowie notfällige Vorstellungen in Praxen, Ambulanzen und Spitälern. It is incomprehensible why additional costs are assumed for anti-CGRP treatment compared to standard therapies. The opposite is true: any successful migraine prophylaxis reduces the cost of acute medication and necessary visits to practices, outpatient clinics and hospitals. 22. Die QALY-Erfassung scheint ausschliesslich auf Schmerzdaten zu beruhen, was für Migräne nachweislich unzulänglich ist. QALY assessment appears to rely solely on pain data, which has been shown to be inadequate for migraine. 23. Die Anwendung auf ein Viertel oder sogar die Hälfte der nach Studienlage in Frage kommenden Patienten ist, wie empirisch belegt, völlig unrealistisch. Zusätzlich ist besonders relevant, dass in der Schweiz derzeit nur Patienten mit mindestens 8 Tagen Migräne pro Monat und Wirksamkeitsnachweis Kostenerstattung erhalten. Die Analyse überschätzt damit die Gesamtkosten und unterschätzt die Kosteneffektivität. The application to a quarter or even half of the patients who are eligible according to the study situation is, as empirically proven, completely unrealistic. In addition, it is particularly relevant that in Switzerland only patients with at least 8 days of migraine per month and proof of effectiveness receive reimbursement. The analysis thus overestimates the total costs and underestimates the cost-effectiveness.	21. As above, migraine management costs are included for CGRP antagonist treatment compared to the comparator. The costs are calculated using modelled headache days, so are less for CGRP antagonist treatment given clinical effectiveness reported in trials. No changes required. 22. As above, QALY calculations are based on migraine days reported in key trials transformed using an algorithm. The limitation of this approach is noted. No changes required. 23. As above, migraine days for EM and CM economic models are in line with Swiss guidelines. The budget impact model assumes the same preventive treatment use and failed therapy assumptions for all patients due to a lack of Swiss data. An additional description of how these uncertainties impact patient numbers will be included in the report.
Teva Pharma AG 24. As mentioned earlier, the selected patient population for EM in the cost effectiveness model (CEM) does not align with the reimbursement criteria in Switzerland, which only covers HFEM (> 8 migraine days). This mismatch could significantly impact the CEM results for EM, as HFEM patients are more similar to CM patients than those with LFEM (< 8 migraine days). 25. According to this HTA, the cost-effectiveness of anti-CGRPs compared to best supportive care (BSC) varies among the different anti-CGRPs. However, there is no summarized overview of the incremental cost-effectiveness ratios (ICERs) for the various anti-CGRPs. We believe that this information is important. Among the anti-CGRPs, fremanezumab (both dosage forms) performs better and that could be highlighted. 26. Furthermore, the budget impact differs depending on the market share of each anti-CGRP. This aspect has not been addressed in the conclusions, but it does influence the overall findings of this HTA.	24. As above, no change required. 25. There are no head-to head comparisons in the clinical evidence, and none should be made in the economic section. CADTH included a statement about the heterogeneity of included trials and robust comparisons cannot be made. This statement is included in the report. 26. Thanks for the feedback. We agree, the budget impact differs depending on the market share of each CGRP antagonist. The future shares are uncertain given these medicines have only recently been listed for reimbursement. This uncertainty is acknowledged in the limitations of the economic analysis of the report. No change required.

5 Comments on ethical, social, legal and organisational issues

Stakeholder / Comment	Author Response
Eli Lilly (Suisse) SA 1. Derzeit dürfen nur solche Patienten mit anti-CGRP-Therapien behandelt werden, die mit den herkömmlichen Präventivmassnahmen nicht behandelt werden können (aufgrund von zuvor dokumentiertem unzureichendem Ansprechen, Kontraindikation oder Therapieabbruch bei Unverträglichkeit, wie in allen „Limitationen“ ausführlich beschrieben). Daher sind anti-CGRP-Therapien für schweizerische Patienten von hoher Relevanz und bieten einzigartige Behandlungsmöglichkeiten. Migräne betrifft 3,7% der Menschen und ist eine sehr belastende Erkrankung mit Auswirkungen auf das persönliche und soziale Leben sowie hohen Kosten für die Gesellschaft (Behinderung am Arbeitsplatz, bei der Betreuung der Familie usw.). Wir möchten betonen, dass in der Schweiz für die Definition und Anwendung von Kosten-Grenzwerten zur Kosten-Nutzen Bewertung im Rahmen von HTA-Protokollen und Berichten derzeit aus unserer Sicht keine Grundlage besteht (vgl. Schreiben vom 12. August 2022). Currently, only those patients who cannot be treated with conventional preventive measures (due to previously documented inadequate response, contraindication or therapy discontinuation due to intolerance, as described in detail in all "Limitations") may be treated with anti-CGRP therapies. Therefore, anti-CGRP therapies are of high relevance for Swiss patients and offer unique treatment options. Migraine affects 3.7% of people and is a very debilitating condition with repercussions on personal and social life and high costs to society (disability at work, in caring for family, etc.). We would like to emphasize that in Switzerland there is currently no basis for the definition and application of cost limit values for cost-benefit assessments in the context of HTA protocols and reports (see letter of August 12, 2022).	1. Thank you for this input, it is noted. No explicit willingness-to-pay thresholds are included in the report. No changes required.
Interpharma (IPH) No comment provided.	N/A
Lundbeck (Schweiz) 2. Patienten dürfen mit Eptinezumab (Vyepti) und den drei anderen CGRP-Antagonisten (aCGRP) gemäss Limitation nur dann behandelt werden, wenn konventionelle Prophylaktika nicht mehr verwendet werden können. Damit sind aCGRP für diese Patienten die einzige pharmakologische Therapieoption und damit Standard of Care. Durch aCGRP wird eine relevante Versorgungslücke geschlossen. Für Patienten in der Schweiz wäre von Vorteil, wenn die Vorgaben der Limitation angepasst und z.B. Therapiewechsel innerhalb der aCGRP bei nichtausreichender Wirksamkeit möglich werden.	2. Thank you for this feedback, it is noted. No changes required.

Wirksamkeit, Sicherheit und Verträglichkeit sind bereits wiederholt von Swissmedic und dem BAG bestätigt; die Wirtschaftlichkeit ist durch SL-Aufnahme sowie die regelmässige Überprüfung sichergestellt. According to the limitation, patients may only be treated with eptinezumab (Vyepti) and the three other CGRP antagonists (aCGRP) if conventional prophylactics can no longer be used. This makes aCGRP the only pharmacological therapy option for these patients and therefore the standard of care. aCGRP closes a relevant gap in care. It would be advantageous for patients in Switzerland if the specifications of the limitation were adjusted and, for example, a change of therapy within the aCGRP was possible if the efficacy was not sufficient. Efficacy, safety and tolerability have already been repeatedly confirmed by Swissmedic and the FOPH; the cost-effectiveness is ensured by SL recording and regular checking.	
Migraine Action 3. Looking only at one part of the costs (direct costs) is hard to understand even if that is the view of the health insurance, although all direct costs (e.g., other treatments and doctor visits due to comorbidities as a result of badly or unmanaged migraine disorder) have to be taken care of by health insurances. BAG might consider as well that society pays for all costs: direct + indirect and even intangible costs. 4. 25 years seem quite high. We do not have data if a long-term treatment is constantly needed, 5. Adherence is always an issue with oral medication so that decreased frequency of dosing is an advantage of CGRP mAbs. 16% adherence after 1 year to 'older' prevention drugs leaves patients 'alone' without treatment and prone to chronification, medication overuse headache including higher comorbidity.	3. Indirect costs are not included in FOPH cost-effectiveness assessments. No change required. 4. Unsure of comment intent. Time horizons are 1, 5 and 10 years in the economic model. No changes required. 5. Clinical effectiveness was taken from key trials, where response rates were used to determine the proportion of patients continuing treatment after 6 months. Longer term discontinuation was included in our models based on lack of efficacy, participant decision and AEs (using the study by Ferrari[163]). A long-term discontinuation probability of 1% is included for all our CGRP models. No change required.
Santésuisse 6. From santésuisse's point of view, these aspects would also have been relevant, but according to feedback on scoping, they were not in the focus of this HTA.	6. Thank you for the feedback. No changes required.
Schweizerische Kopfwehgesellschaft (SKG) 7. It is intriguing from an ethical perspective to compare cost-effectiveness of two treatments, anti-CGRP vs. BSC, when access to one of these treatments, anti-CGRP, is conditional on failure in SOC. Regarding the debilitating nature of migraine and the associated loss in quality of life, such a scenario is cynical and raises ethical and legal questions. 8. The authors explicitly point out that they were only mandated to analyze direct costs. This is not only a highly questionable perspective for any institution caring about societal impact of disease, it moreover introduces a strong negative bias when comparing cost-effectiveness of any treatment in migraine with that of treatments for other diseases. This is because in migraine, indirect costs are 5 to 10-fold the amount of direct costs whereas in most other diseases their share is typically less than half of the entire costs.	7. Thanks for your feedback. The cost-effectiveness analysis compares the use of CGRP antagonists versus standard of care using trials where rescue medicines were permitted in both arms. No change required. 8. Indirect costs are not included in FOPH cost-effectiveness assessments. No change required.

Schweizerische Neurologische Gesellschaft (SNG) 9. Der Auftrag an die Autoren der Analyse schliesst die Einbeziehung indirekter Krankheitskosten explizit aus. Anders als bei anderen Erkrankungen betragen bei Migräne die indirekten Kosten ein Vielfaches der direkt das Gesundheitssystem betreffenden Kosten. Aus einer Perspektive gesamtgesellschaftlicher Kostenverantwortlichkeit ist dieser Ausschluss indirekter Kosten nicht nachvollziehbar. Ausserdem wird damit die Vergleichbarkeit der Ergebnisse mit Werten für Behandlungsverfahren bei anderen Erkrankungen systematisch zuungunsten der Migräne verzerrt. The commission to the authors of the analysis explicitly excludes the inclusion of indirect medical expenses. Unlike other diseases, the indirect costs of migraine are many times the costs directly related to the healthcare system. This exclusion of indirect costs is incomprehensible from the perspective of society as a whole being responsible for costs. In addition, the comparability of the results with values for treatment methods for other diseases is systematically distorted to the disadvantage of migraine. 10. Die Analyse vergleicht Behandlungen mit klassischen Medikamenten mit einer Behandlung, die in der Schweiz nur erstattet wird, wenn diese Verfahren versagt haben und der Nachweis der Wirksamkeit geführt wird. Wir halten diesen Ansatz für rechtlich und ethisch fragwürdig. The analysis compares treatments with classic drugs with a treatment that is only reimbursed in Switzerland if these procedures have failed and their effectiveness can be proven. We consider this approach to be legally and ethically questionable.	9. Indirect costs are not included in FOPH cost-effectiveness assessments. No change required. 10. The majority of included clinical studies compared CGRP antagonists to placebo, noting that rescue medications were often permitted in both arms. As above, the cost-effectiveness analysis compares the use of a CGRP antagonist versus standard of care using trials where rescue medicines were permitted on both arms. No change required.
Teva Pharma AG 11. This HTA presents projections for the uptake of anti-CGRPs at 10%, 25%, and even 50% by 2026. However, we question the realism of even the 10% scenario, as the market is likely to become saturated in the near future, leading to non-linear growth. Even considering the LFEM population, the projected total population in 2026 appears unrealistic. This incorrect estimation affects the evaluation of the total population of EM and CM patients who have failed two or more preventive treatments and results in LFEM patients being deprived of treatment with anti-CGRPs. Additionally, it is important to note that the market will not be exclusive to anti-CGRPs, other treatment becoming available, which will also impact their uptake. 12. Anti-CGRPs have been available for approx. 4 years and next to this HTA are soon to undergo a third review by the FOPH. The repeated examination of the same data within a short timeframe is time-consuming and resource intensive as no new outcomes can be expected.	11. Costing scenarios are limited to data availability. Hypothetical scenarios using preventive medicine use and failed preventive treatment were based on similar assumptions being applied to all migraine patients. The uncertainty associated with LFEM, market saturation and market shares, along with new products will be discussed in the budget impact uncertainty section. 12. Thank for your feedback. No changes needed.

6 Comments on the discussion and conclusions

Stakeholder / Comment	Author Response
Eli Lilly (Suisse) SA 1. Insgesamt bestätigt dieser HTA-Bericht die Kosteneffizienz der anti-CGRP-Therapien, wenngleich wir der Ansicht sind, dass der Bericht die Realität nicht vollständig wiedergibt. Overall, this HTA report confirms the cost-effectiveness of anti-CGRP therapies, although we believe the report does not fully reflect reality.	1. Thank you for the feedback. The HTA summarises the best available evidence as it applies to Swiss practice, noting there are limitations in the applicability of the evidence. No changes to the report needed.
Interpharma (IPH) No comment provided	N/A
Lundbeck (Schweiz) 2. Durch aCGRP wurden relevante Versorgungslücken geschlossen; zu wünschen ist, dass bestehende Limitationen verringert und z.B. Therapiewechsel innerhalb der aCGRP bei nichtausreichender Wirksamkeit möglich werden. Eptinezumab ist als einziger aCGRP gezielt zur Gabe per Infusion entwickelt. Hierdurch resultieren Vorteile für die Versorgung: Ärzte haben die Therapiehoheit und können z.B. die korrekte Anwendung sicherstellen; dies kann für Patienten wichtig sein, die Probleme bei der Selbstanwendung mit den anderen aCGRP haben oder nur eingeschränkt compliant sind. Die Infusionsdauer von 30min ermöglicht die intensive Interaktion mit den Patienten, um u.a. therapeutische Maßnahmen zu besprechen und den Behandlungserfolg zu bewerten. Die 12-wöchige Wirkdauer sichert die Adhärenz über einen längeren Therapiezeitraum. Grundsätzlich bedeutend für das HTA ist, dass möglichst aktuelle Daten einbezogen und die Bewertungs- und Berechnungsverfahren transparent dargestellt werden. Relevant supply gaps were closed by aCGRP; It is desirable that existing limitations are reduced and that, for example, a change of therapy within the aCGRP becomes possible in the event of insufficient effectiveness. Eptinezumab is the only aCGRP specifically developed for administration by infusion. This results in advantages for the supply: Doctors have the therapy sovereignty and can, for example, ensure the correct application; this may be important for patients who have problems self-administering the other aCGRP or have limited compliance. The infusion duration of 30 minutes enables intensive interaction with the patient in order to discuss therapeutic measures and evaluate the success of the treatment, among other things.	2. Thank you for this feedback, it is noted for consideration by the Commission. On the recency of the results, an updated systematic literature search (9 Feb 2023) and economic evaluation was conducted prior to the stakeholder feedback round to alleviate any concerns regarding the currency of the results from the original search (9 March 2022). No changes to the report are needed.

The 12-week duration of action ensures adherence over a longer period of therapy. It is fundamentally important for the HTA that data that is as up-to-date as possible is included and that the assessment and calculation procedures are presented in a transparent manner.	
Migraine Action 3. Requirements for migraine prophylaxis: - Rapidly effective for EM, CM + MO with predictor if possible. - Without severe side effects in long-term therapy. - High patient acceptance. - No pharmacological interactions, can be optimally combined with de-escalating acute medications. - No up-dosing, no daily intake. - No central nervous restrictions; ideal as a basis for non-drug active therapies (e.g. sports). - Does not make patients tired, weight neutral; no worsening of depression +anxiety - CGRP's address this request, erenumab had superior tolerability and efficacy profile than topiramate, with less treatment discontinuation over 24-week treatment phase. - Instead of price reduction, models like :reimbursement only after first 3 months positive outcome or only if accompanied by a stakeholder collaborative patient program with evidence based health outcome. - An optimal preventive therapy manages the course +pathogenesis of migraine and prevents comorbidities by improving health literacy and QOL.	3. Thank you for providing this feedback, it is noted for consideration by the Commission. No changes required.
Santésuisse 4. The discussion and conclusion provide a good summary of the current state of knowledge on the CGRP antagonists used today. It is welcomed that currently available guidelines, position papers and HTAs were included and discussed. In addition, some studies are still planned. We hope that certain questions can be clarified (duration of therapy, comparison to other available therapies etc.). Due to the various gaps in knowledge, the HTA presented here is a first compilation of the current data. However, it must be continuously supplemented with new findings so that it can serve as an important basis for the regular review of the WZW of CGRP antagonists.	4. Thank you for providing this feedback. No changes required.
Schweizerische Kopfwehgesellschaft (SKG) 5. It is fairly trivial to state that cost-effectiveness increases if medication costs less. It is equally trivial to state that cost-effectiveness of a preventive medication increases the greater underlying disease activity. It is surprising that the authors would not detail and explain why	5. Thanks for the feedback. The cost-effectiveness of CGRP antagonists versus BSC ranged from Swiss francs (CHF)134,152 to CHF318,982 per QALY gained over an analysis period of 1-year among episodic migraine patients, and CHF53,067 to CHF84,033 per QALY gained among chronic migraine patients.

their analysis provides by far the least favorable cost-effectiveness outcome of the so far existing analyses. Instead, the authors claim their estimations to be well aligned to those obtained in other analyses. This may be true given the degree of uncertainty and hence lack of precision in such modelling.	Our results are similar to the results of the reanalyses of the chronic migraine model submitted for CADTH review, which had a 5-year time horizon. Erenumab 140 mg was calculated to have an ICUR of CAD66,359 (CHF45,245) per QALY gained, although erenumab 70 mg was extendedly dominated in the sequential analysis. For the EM model, the ICER erenumab 140 mg was $153,635 (CHF 102,864) per QALY and erenumab 70 mg was extendedly dominated in the sequential analysis. For fremanezumab, CADTH reviewers undertook a series of reanalyses, with costs related to hospitalisation being removed and the time horizon being reduced to 5 years. The episodic migraine patient ICER was CAD164,243 (CHF118,544) per QALY (incremental cost CAD13,571, QALYs 0.08) compared with best supportive care, while the chronic migraine patient ICER was CAD128,950 (CHF93,071) per QALY (incremental cost CAD13,436, incremental QALYs 0.10) compared with best supportive care. For galcanezumab, CADTH undertook a re-evaluation for episodic migraine patients who had used ≥2 prior preventive migraine therapies, which resulted in an additional cost of CAD14,563 and 0.053 additional QALYs over best supportive care over 5 years. This resulted in an ICER of CAD273,560 (CHF197,445) per QALY gained. The re-evaluation for chronic migraine resulted in an additional cost of CAD18,247 for galcanezumab and 0.167 additional QALYs compared to best supportive care, corresponding to an ICER of CAD109,325 (CHF78,906) per QALY gained.
Schweizerische Neurologische Gesellschaft (SNG) 6. Die Autoren stellen fest, dass die Kosteneffektivität um so höher ist, je mehr Tage pro Monat durch die Erkrankung betroffen sind. Sie stellt weiterhin fest, dass Kosteneffektivität zunimmt, wenn der Preis des Medikamentes abnimmt. Beide Aussagen sind offensichtlich richtig, aber ebenso offensichtlich trivial und hätten nicht diese aufwändige Analyse benötigt. The authors find that the more days per month affected by the disease, the higher the cost-effectiveness. She also notes that cost-effectiveness increases as the price of the drug decreases. Both statements are obviously correct, but also obviously trivial and would not have required this complex analysis. 7. Was weniger trivial bleibt, ist die Frage warum die vorliegende Analyse im Vergleich zu allen anderen vorliegenden berichten die deutllich schlechteste Kosteneffektivität ermittelt. Die Autoren beschreiben ihre Ergebnisse zwar als sehr ähnlich mit den vergleichbaren, aber das kann nur zutreffen, wenn die Unsicherheitsmargen solcher Schätzungen extrem hoch und damit die Ergebnisse letztlich unzuverlässig sind.	6. Thank you for the feedback. No change needed. 7. As above, results are in line with CADTH re-evaluations. No change needed.

What remains less trivial is the question of why the present analysis determines the clearly worst cost-effectiveness compared to all other available reports. Although the authors describe their results as very similar to comparable ones, this can only be true if the uncertainty margins of such estimates are extremely high and the results are ultimately unreliable.	
Teva Pharma AG 8. The implications of this HTA remain unclear. It is evident that both EM and CM patients benefit from prophylactic treatment with anti-CGRPs, leading to an improvement in their quality of life. However, it is important to note that anti-CGRPs are not reimbursed in Switzerland for LFEM patients. Additionally, we believe that the projected uptake scenarios are not realistic even including LFEM patients, as the market for anti-CGRPs does not grow linearly and will soon face competition from other prophylactic treatments. 9. We want to highlight that the strict reimbursement criteria also result in additional healthcare costs, such as mandatory therapy breaks after one year of treatment. However, this aspect has not been discussed in the HTA. 10. Also, indirect costs such as non-productive time due work absences have not been included in the calculations.	8. The economic analysis was undertaken for EM and CM patients with starting MMDS of 9 and 18 days per months. These baseline MMDs are in line with Swiss reimbursement and taken from key clinical trials. Effectiveness data for the LFEM patient group are required for economic modelling for this specific population. Cost scenarios are included for budget impact analyses. There are a range of uncertainties given limitations around Swiss medicines usage amongst different populations groups and projected market shares given CGRP antagonists have only been recently listed. We agree that CGRP antagonist uptake may not grow linearly and will soon face competition from other prophylactic treatments. These considerations will be included in the description of uncertainty in the budget impact section. 9. There is uncertainty about mandatory therapy breaks after one year of treatment which impacts budget analysis. A range of uptake scenarios have been included. This break was included in longer term projections (5 and 10 year) in the economic sensitivity analysis section. Other assumptions, such as choice of comparator and migraine day reductions associated with non-response had a large impact on results. No change in the report to be included. 10. See past comments regarding indirect costs.