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LETTER TO THE EDITOR

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# Novel acute therapies in the treatment of migraine: impact of re-dosing on cost–utility outcomes

Recently, several novel therapies have been developed for acute treatment of migraine, all of which have shown considerable efficacy benefits over placebo[1]. Novel therapies include the calcitonin gene-related peptide (CGRP) receptor antagonists rimegepant (NURTEC ODT, Biohaven, New Haven, CT)[2] and ubrogepant (UBRELVY, Allergan, Dublin, Ireland)[3,4] and the 5HT-receptor agonist lasmiditan (REYVOW, Eli Lilly, Indianapolis, IN)[5]. The design of pivotal trials for these therapies include a key difference, in that the rimegepant phase III program only allowed for a single dose of study medication, while ubrogepant and lasmiditan trials both allowed for re-dosing: for ubrogepant, 37.6% of patients received a second dose (ACHIEVE)[3] and for lasmiditan 33% of patients required re-dosing (SAMURAI and SPARTAN)[5].

The Institute for Clinical and Economic Research (ICER) conducted an evidence review in acute treatment for migraine, including network meta-analysis (NMA) and economic evaluation of rimegepant, ubrogepant, and lasmiditan in two distinct populations: triptan-eligible patients for whom sumatriptan and eletriptan were included as comparators, and a triptan-refractory or intolerant population for whom triptans were not included as comparators[1]. This correspondence is focused on the second, triptan-ineligible population, which is anticipated to be more relevant for novel therapies. In brief, in the ICER economic evaluation, a *de novo* semi-Markov decision-analytic model was used from a US health sector payer perspective with a 3% annual discount applied to compare rimegepant, ubrogepant and lasmiditan[1]. The NMA included four randomized controlled trials of rimegepant, three randomized controlled trials of ubrogepant and three randomized controlled trials of lasmiditan[1]. Patients that participated in these trials were allowed to discontinue treatment if it was not sufficiently effective or if they experienced intolerable adverse effects[1]. Freedom from pain at two hours after treatment and pain relief were the primary and secondary efficacy endpoints, respectively, in all the trials[1]. The outcome measure of the ICER economic evaluation was incremental cost–utility ratio (ICUR) per QALY gained, which was dependent on the pricing of the treatments[1]. EQ-5D migraine-specific utility values, stratified by migraine severity, were obtained from published literature, and wholesale acquisition costs with an industry-average 27% discount applied were used where available to calculate treatment costs[1]. A two year time horizon was chosen because it was believed that it would be long enough to allow for stable ICER estimates for acute treatment, since migraine has a rapid onset and treatment benefits are observed rapidly as well[1].

Of note, while ICER did consider a number of sensitivity and scenario analyses in addition to the base case, none of these analyses addressed the issue of re-dosing for ubrogepant or lasmiditan. Thus, while efficacy results for these drugs were taken from trials in which more than 30% of patients took a second dose of study medication (in contrast to rimegepant for which only a single dose was allowed per attack), the cost-effectiveness analysis conducted by ICER included the costs of a single pill for each comparator.

Under these assumptions, and based on differences in pain trajectories observed across comparators, the cost-effectiveness ratios reported vs. placebo/usual care were: $39,800 for rimegepant, and $40,000 for ubrogepant, with negligible differences related to two-hour NMA outcomes and safety profiles, and $151,800 for lasmiditan[1]. While the final ICER report does not include sufficient data to disaggregate total drug costs (accounting for discontinuation) from other costs in the overall totals, simplifying assumptions were made to estimate drug costs. In the ICER analysis, published lasmiditan discontinuation rates were applied to all novel therapies, with an estimated 21.8% of patients discontinuing related to effectiveness (in the first year only) and 12.8% per year due to adverse events[1]. Under the assumption that both discontinuation rates are applied at the midpoint of the year, the resulting time on therapy is estimated to be approximately 1.4 years in a 2.0-year period. Based on this assumption, the proportion of total costs related to drug costs within the model could be estimated, allowing for the calculation of alternative cost-effectiveness results for adjusted dosing assumptions.

If the ubrogepant and lasmiditan costs are adjusted upward by 37.6% and 33%, respectively, the drug costs increase correspondingly, such that total costs increase from $12,000 to approximately $13,552 for lasmiditan, and from $10,660 to approximately $12,500 for ubrogepant. This results in incremental cost-effectiveness ratios vs. usual care of $271,500 for lasmiditan and $163,000 for ubrogepant, while the ratio of $39,800 for rimegepant remains constant. As rimegepant is associated with equivalent or higher QALYs and lower costs than the other novel therapies, it is found to be economically dominant to ubrogepant and lasmiditan, respectively.

While any economic assessment across the three novel products is subject to limitations, particularly as they have not been studied head-to-head such that use of indirect treatment comparisons and consequent assumptions are required. All trials measured treatment effects for a single migraine attack, and long-term outcomes were not assessed. There is a significant amount of uncertainty regarding base

case estimates regarding the impacts of therapies on pain relief more than 2 h after treatment, on emergency room visits and hospitalizations, and the impact of re-treatment on migraine frequency[1].

With respect to lasmiditan re-dosing, the SAMURAI and SPARTAN trials both allowed for re-dosing in the first 24 h[5], and it is this re-dosing that is used to adjust medication cost in the revised analysis. However, the current product label for lasmiditan explicitly warns to not re-dose within 24 h[6]. For the purposes of the re-analysis presented here, it is assumed that similar rates of re-dosing as observed in the SAMURAI and SPARTAN trials would occur in real-world settings, but between 24 and 48 h following original dose, rather than within 24 h. Based on the monograph warning, there may be a lower rate of re-dosing observed in practice, although efficacy rates would then be expected to be affected accordingly. In the absence of other data and for consistency in data sources, trial-based re-dosing and efficacy were thus assumed here.

When the impact of re-dosing is taken into account, rimegepant is associated with more favorable cost-effectiveness results vs. usual care compared to ubrogepant and lasmiditan. These findings may be relevant for other cost-effectiveness analyses, and may ultimately impact reimbursement policies and influence patient choice and access to more acute treatments for migraine.

## Transparency

### Declaration of funding

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### Declaration of financial/other relationships

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### Contribution statement

All coauthors collaborated on the following elements of the work: conception and study design, data acquisition, analysis & interpretation of data, manuscript draft and review, and final approval of completed manuscript.

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