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Japan's CEA Scheme: How It Works And Impact So Far

Average 2.7% Cut

by Lisa Takagi

Japan has announced the latest evaluation results under its cost effectiveness assessment scheme. But how does it work and how much have prices been revised so far under the four-year-old program following discussions between pharma firms and authorities?

Japan's Economic Effectiveness Price Cut Scheme (□□□□□□□□□), a system of cost effectiveness assessment (CEA) for drug reimbursement under the country's national health insurance (NHI) program, has now entered its fourth year with a new list of drugs coming under evaluation.

The program has resulted mostly in price cuts on already launched products every year since 2019, in addition to those imposed as part of Japan's regular price revisions with the purpose of balancing budgets and health spending under the NHI.

The latest CEA results in November notably cut the tariff price of *argenx N.V.*'s neonatal Fc receptor blocker for myasthenia gravis Vyvgart (efgartigimod alfa) by nearly 8% around 18 months after its launch. Looking ahead to another high-profile candidate, the scheme is also expected to evaluate *Eisai Co., Ltd.*/*Biogen, Inc.*'s Alzheimer's drug Leqembi (lecanemab) considering its impact on nursing care costs after its initial price is announced. (Also see "*Japan Approves Leqembi, All Eyes Now On Extended Pricing Discussions*" - Pink Sheet, 2 Oct, 2023.)

In this analysis, the *Pink Sheet* takes a look at how the scheme has worked so far, its latest outcomes and the list of the drugs undergoing evaluation as of November 2023.

Evaluation After Initial Price Listing

The CEA scheme was introduced in April 2019 for the purpose of "complementing Japan's drug pricing system" by adding another price evaluation option to help maintain the financial balance within the NHI reimbursement tariff. 32 drugs and two medical devices have so far completed the evaluation, resulting in an average 2.7% cut across the drug products.

Oncology drugs accounted for the single biggest category (9/32) and the biggest single price cut to come out of the system was 9.4% in June 2023 for *Insmed Incorporated*'s Arikayce (amikacin) for non-tuberculosis mycobacteria infections.

It is applied to products meeting several conditions: price-listed after April 2019 awarded a premium for innovativeness (XXXXX) or premium for usefulness (XXXXX); an official peak annual sales forecast of JPY5-10bn ($34-68m) or more than JPY10bn, or a "significantly high reimbursement price"; listed before April 2019 with a premium for innovativeness or premium for usefulness and forecast peak sales of JPY100bn or reimbursement prices "considered as extremely high" by a Ministry of Health, Labour and Welfare committee.

The CEA evaluation will start immediately after first price listing if a product's peak sales forecast exceeds JPY10bn or if its reimbursement price is considered high. Competitor products matching the same conditions should also be evaluated under the scheme.

The evaluation process excludes therapeutics used exclusively to treat rare diseases with limited treatment options, or therapeutics for pediatric use only. The CEA committee will also consider mitigating any price cut decisions for cancer drugs and therapeutics for rare or pediatric diseases.

Since its launch, the scheme has resulted in recommended price cuts several times per year since 2021, all of which have been adopted by the ministry; the first were for two CAR T-cell therapies. *Kite Pharma, Inc.*/*Daiichi Sankyo Co., Ltd.*'s Yescarta (axicabtagene ciloleucel) obtained its first Japanese approval in January 2021 for relapsed/refractory diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed follicular lymphoma or high-grade B cell lymphoma.

Bristol Myers Squibb Company's Breyanzi (lisocabtagene maraleucel) was approved in March 2021 for relapsed/refractory large B-cell lymphoma and R/R follicular lymphoma after two or more lines of therapy. The CEA evaluation cut the prices of both drugs by 4% from JPY34.1m to JPY32.6m, in April 2021 for Yescarta and the following month for Breyanzi.

Timing, Process, Cuts

The CEA scheme's entire selection and evaluation process usually takes 14 to 18 months. A dedicated MHLW committee, comprising external insurance, medical and legal experts and a smaller number of industry specialists, select the products to be evaluated and notify the relevant company.

Then firms will then discuss with the National Institute of Public Health the proposal for each individual product's evaluation of cost and efficacy in comparison with a competitor, which requires the approval of the dedicated committee.

The company will then run its own analysis and submit a report to the committee, which will also conduct its own separate analysis to decide which report is "more reasonable" in deciding whether to cut or increase the price, by how much.

The maximum price cut resulting from CEA assessment is 15%, although the range may vary and there may be cases where the decision is to leave prices unchanged. Also, a cut would be limited to within 10% if a product was awarded a lower than 25% premium as part of its initial pricing, and limited to within 15% if the pricing premium was over 25%, the MHLW notes.

Once any price cut is determined as part of the CEA process, the new reimbursement price would usually be effective within three months of the official announcement.

Vyvgart Cut By 8% After Debate

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The latest results issued in November show products approved from September 2021 to March 2022 were evaluated.

The MHLW decided to maintain prices for *UCB S.A.*'s IL-17A/F inhibitor Bimzelx (bimekizumab), *Idorsia Pharmaceuticals Ltd*'s endothelin A receptor antagonist Pivlaz (clazosentan) and *AstraZeneca PLC*'s reversal agent for FXa inhibitors Ondexxya (andexanet alfa).

On the other hand, the evaluation resulted in slight price cuts for *Eli Lilly and Company*'s RET kinase inhibitor Retevmo (selpercatinib) and *Neurocrine Biosciences, Inc.*/*Mitsubishi Tanabe Pharma Corporation*'s vesicular monoamine transporter type 2 inhibitor Dysval (valbenazine). Vyvgart was given a 7.8% reduction.

The MHLW documents on Vyvgart show contrasting views between argenx and the ministry over an appropriate comparator. The product obtained its first Japanese approval last year for generalized myasthenia gravis with insufficient response to steroids or non-steroidal immunosuppressive therapies. (Also see "*Argenx Enters Japan With Smooth Approval – How Was It Possible?*" - Scrip, 10 Jun, 2022.)

The Belgian firm claimed the first-in-class drug's cost performance should be compared with a combination of intravenous immunoglobulin, plasma exchange and AstraZeneca/*Alexion Pharmaceuticals Inc.*'s Soliris (eculizumab). The ministry said it had run an analysis for each of

these treatments.

However, the MHLW concluded the comparative analysis should use a combination of prednisolone, immunosuppressant and an acetylcholinesterase inhibitor, as it would give “higher certainty.” It also pointed out Japan may not have many actual use cases for Soliris in myasthenia gravis.

While the CEA assessment is designed to consider reports from both the pharma firm and ministry, in the latest six cases, the MHLW committee concluded it was "more reasonable to consider" the ministry’s own public analysis rather than that submitted by the manufacturer.

Zolgensma, Lagevrio, Xocova On Current List

The latest list shows 14 drugs are currently undergoing the CEA evaluation process in Japan. *Novartis AG*’s gene therapy for spinal muscular atrophy Zolgensma (onasemnogene abeparvovec) was selected because of its extremely high reimbursement price. But its evaluation has been in hiatus as the MHLW acknowledged the need to collect long-term efficacy data until 2026 to inform the evaluation.

Most of the others on the list were selected as their peak sales are forecast to exceed JPY10bn. COVID-19 therapeutics Lagevrio (molnupiravir) from *MSD* and Xocova (ensitrelvir) from *Shionogi & Co. Ltd.* are also currently under evaluation.

There are also several drugs that obtained their first Japanese approval this year, including Phozevel (tenapanor) from *Kyowa Kirin Co., Ltd.*/*Ardelyx Inc.* and *Pfizer Inc.*’s Litfulo (ritlecitinib).

Considering the huge demand for GLP-1 receptor antagonists for diabetes and obesity, Eli Lilly and Company’s Mounjaro (tirzepatide) and *Novo Nordisk A/S*’s Wegovy (semaglutide) are also being evaluated. (Also see "*Japan Pricing Update: Wegovy Finally Listed, Upcoming Special Cuts For Imfinzi, Polivy*" - Pink Sheet, 22 Nov, 2023.) (Also see "*Japan Faces GLP-1 Shortage As Off-Label Diet Use Surges*" - Pink Sheet, 16 Aug, 2023.)

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Looking Ahead

Official discussions have been continuing since 2021 on how to improve Japan's standard reimbursement pricing scheme and the composition of the committee for CEA evaluation. Ministry documents suggest these will continue over 2024, including regular hearings involving the biopharma industry.

With the recent Japanese approval of Leqembi, the CEA scheme is now having to grapple with

the question on whether to expand its scope to a consideration of impact on nursing care and related costs. Eisai/Biogen have requested the MHLW to consider this if the drug is evaluated.

Although Leqembi's launch reimbursement price has not been announced yet (it is expected by the end of December), an official document dated 15 November notes this will "indicate the certain direction for [Leqembi's] CEA evaluation by the announcement of its pricing."