What is the European market access (pricing and reimbursement) process and what key factors does Amarin believe will make it successful in achieving timely and adequate reimbursement in Europe?

Amarin believes that there are five important commercial considerations to a medicine being successfully launched in Europe: 1) large unmet medical need; 2) established safety and efficacy with differentiation from potentially competitive therapies; 3) regulatory approval; 4) market access; and 5) effective product-related education and awareness. While aspects of these five considerations overlap, in many respects they are sequential.

With regard to large market opportunity, there is no approved therapy on the market today in Europe for addressing persistent cardiovascular risk (the cardiovascular risk which exists beyond cholesterol management) in statin-treated patients with elevated triglycerides, despite the fact that there are millions of people in Europe with such persistent cardiovascular risk.

The safety and efficacy of icosapent ethyl has been established through more than a decade of clinical study, including the successful results of the landmark REDUCE-IT® cardiovascular outcomes study. The second highest enrolling country in that large-scale study (after the U.S.) was from Europe (The Netherlands).

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications for centralized marketing authorizations in the European Union. This authorization procedure allows pharmaceutical companies to submit a single marketing authorization application (MAA) seeking to market the medicine throughout all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

Amarin's MAA with the EMA was accepted for review in December 2019. On January 28, 2021, the Committee for Medicinal Products for Human Use (CHMP) of the EMA adopted a positive opinion, recommending that a marketing authorization be granted to icosapent ethyl in the European Union for cardiovascular risk reduction under the brand name VAZKEPA®, known in the United States under the brand name of VASCEPA. The CHMP recommendation is now expected to be reviewed by the European Commission within 67 days of this opinion. With regulatory approval expected in April 2021, the company is preparing for market access and commercial launch.

After the European Commission's decision to grant marketing authorization, the market access process can be formally launched based on the approved label for the drug. In advance of regulatory approval and receipt of the label, there are certain preparatory market access actions that can be taken, although these vary by country. Amarin has been pursuing such pre-label consultation steps where permitted.

Market access in Europe is managed on a country-by-country basis. European country reimbursement (coverage) for innovative therapies are almost exclusively covered through public national funding and not individual private insurance companies.

Pricing and reimbursement of cardiometabolic products in Europe is both complex and challenging. The market access process is evaluated by each country independently through country-specific regulated national procedures. Procedures vary by country but generally take a 2-step approach:

- Step 1: National agencies in each country assess product data and decide on inclusion into the national reimbursement system for public funding (coverage). National agency review includes assessment of efficacy and safety data to understand the need and value of a new medicine.
- Step 2: National agencies in each country use the benefit evaluation concluded from the national agency review, along with other economic parameters, to define the reimbursed price in that specific county. In this step they typically review country-specific demographic information to quantify and assess the value of the new medicine on patient care and the financial impact of the new medicine on healthcare spending. This step includes review of cost effectiveness data of the medicine and cost effectiveness of alternative treatments, if any. They may look at the consequences of not treating patients as well as the pricing of comparable products, if any. The price negotiations vary in requirement and timeline by country, which is why new medicines obtain coverage and reimbursement at different time points.

Consequently, time to market access for each EU country will vary significantly by market. Some countries, such as Germany, grant rapid access during an initial 12-month period while the final price is negotiated based on the price submitted by the medicine sponsor. The 12-month period commences upon this initial price submission by the medicine sponsor. After marketing authorization is granted, the sponsor decides when to submit the price to the German authorities, thus initiating the 12-month period. Under this construct, it is intended that by the end of the 12-month period a new negotiated price between the medicine sponsor and the national agency will apply for continued marketing and sales in Germany. Other countries, such as Spain and France, usually take more than 12 months after marketing authorization. Timing varies from medicine to medicine based on multiple factors such as the strength of the data, availability of alternative treatments and the pricing sought by the sponsor company.

The application for market access is submitted in the form of a reimbursement dossier containing key sections that national payers will evaluate and may include:

- a description of the unmet need in the label population (limitations of existing treatment options);
- proof of clinical efficacy and health benefits for these patients compared to the standard of care;
- pharmacoeconomic data such as cost effectiveness and budget impact models.

After a reimbursement application is submitted in a specific country, the market access process often includes opportunity for direct dialogue between the sponsor (e.g., Amarin) and the national agencies, which focus on ensuring that questions are answered and provide opportunities to reinforce important points. During the review process by national agencies, input from external stakeholders (leading specialists, patient groups) can be sought.

We believe Amarin is well positioned to achieve market access in Europe and receive reasonable prices for several reasons:

- Amarin has clinical trial outcomes trial data demonstrating the effectiveness of VAZKEPA®, in reducing cardiovascular events, like strokes, heart attacks and cardiovascular death, in patients with persistent cardiovascular risk. As per prior assessments of highly innovative medicines, European payers strongly value health benefits as evidenced by outcomes data.
- Cost effectiveness of a new therapy is important. The relative number needed to treat, as demonstrated and published in the REDUCE-IT cardiovascular outcomes study of VAZKEPA, compares favorably to other therapies. While there is no approved medicine in Europe for the persistent cardiovascular risk indication being sought for VAZKEPA, it is important that the

number needed to treat for VAZKEPA is relatively low. National agencies are given limited budgets for healthcare and medicine spending overall. As a result, these national agencies tend to prioritize reimbursement of medicines with positive pharmacoeconomic profiles that provide high "value for money." Various reports, such as ICER (here) in the US and CADTH in Canada demonstrate a clear case that VAZKEPA is cost effective in those respective geographies on a standalone basis and compared to existing therapies. Such existing analysis can be referenced by EU national agencies while country-specific analysis is being prepared to support the market access process.

- The economic burden of cardiovascular disease is high in Europe and reducing the incidence of these events represents an opportunity for cost savings related to cardiovascular events avoided.
- Amarin is pursuing market access for VAZKEPA in Europe for the treatment of persistent cardiovascular risk with the existing support of key medical associations such as the European Society of Cardiology and the European Atherosclerosis Society. Such support should enhance Amarin's efforts for favorable market access and adoption.

If a country refuses reimbursement of a medicine or price negotiations fail to conclude on a timely basis, it is possible to appeal or resubmit a new application for reimbursement in that specific country.

In both the United States and Canada, reimbursement uptake was relatively prompt after regulatory approval of VAZKEPA for reduction of persistent cardiovascular risk reduction. In Europe, as in Canada, the indication being pursued is for the treatment of studied patients with persistent cardiovascular risk where the costs incurred for not treating such patients is high. Amarin believes it is well positioned as there are no other proven therapies for this indication and VAZKEPA is supported by long-term clinical outcomes data and the support of leading medical societies in Europe and globally through their adoption of guidelines and position statements that support VAZKEPA use in the indication sought.

During the period of negotiation of medicine pricing in Europe, as is true for most negotiations, little information will likely be available. Once medicine reimbursement and pricing is approved in European countries, list prices are publicly disclosed in assessment reports.

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