PERSPECTIVE

Increasing Use of Compassionate Use/Managed Access Channels to Obtain Medicines for Use in COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic has triggered an extensive need for new therapeutics and there has been widespread use of unapproved/repurposed medicines. Several countries have regulations for access to unapproved medicines, known as compassionate use, managed/expanded access or emergency use. The Novartis Managed Access activity for COVID-19 delivered unapproved/repurposed medicines to nearly 6,000 patients over a 6-month period. With the rapid growth of such access mechanisms to address COVID-19, a better understanding of these channels is required.

Response to the COVID-19 global pandemic has generated unprecedented focus and investment in developing new therapeutics, vaccines, and diagnostics. These efforts have included the use of unapproved medicines and repurposing of existing therapies, which could be of clinical benefit. Even though many of these products are moving through accelerated clinical trials and regulatory reviews, there is understandable pressure to provide access as soon as possible to address urgent patient needs.

We report on the role of various channels currently utilized to access repurposed or unapproved medicines to address the COVID-19 pandemic. For unapproved medicines, many countries have regulations for pre-approval access, referred to as "compassionate use," "expanded access," "named patient supply," "special access," or similar terms.[1-4] For the unapproved use of repurposed medicines, some countries allow physicians unfettered discretion to prescribe these as per normal clinical practice, or include the access provision within their compassionate use regulations or "emergency use" frameworks (which may include drug donations). However, some countries have no regulatory provisions at all in this context.[2] At Novartis, all such access mechanisms for unapproved or unavailable medicines are handled under the umbrella term "Managed Access Programs" (MAPs).[5]

Generally, MAPs make available selected products from a company's portfolio, which are unapproved or locally unavailable to support patients with a serious or life-threatening condition, who meet certain medical and other defined criteria as per local regulations. These criteria usually include ineligibility to enroll in or access a clinical trial, and the absence of any comparable alternative treatment options. Such programs typically involve therapeutic products, which are still "investigational" (i.e., not yet approved by any regulatory authority), and may involve products that already have a major regulatory approval elsewhere (e.g., from the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA)).

In general, unsolicited requests for these products are made by a patient's treating physician (or healthcare professional) and reviewed by the company. This review considers the patient's disease or condition, and the benefit-risk profile of the product requested in terms of safety and efficacy, based on clinical trial data and overall scientific evidence available at the time of the request. Although limited patient outcomes data may be collected in MAP programs, it is worth emphasizing that a randomized controlled trial is the gold standard for evidence generation to fully elucidate the safety and efficacy of any product.

Managed Access in most countries can either be handled on an individual patient basis ("individual patient request") or through a group or cohort program set up by the manufacturer or, in some cases, a physician or healthcare institution. For an individual patient request, most country regulations require that the treating physician submit the request to the Health Authority (HA) for approval either prior to or after submission to the manufacturer for approval and agreement to supply the product. For a cohort program, following

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availability of sufficient scientific evidence usually from a phase IIb or III trial, a manufacturer may decide to open a program, and will need to submit a Treatment Plan/Protocol to a country's HA. Following HA approval of the cohort, the program is available to patients in that particular country, and physicians can subsequently place independent requests directly to the manufacturer.

At Novartis, requests can be made via our online submission portal, which is part of an end-to-end request management system designed to make the application process more streamlined for requesting physicians. The system offers an easy-to-complete online form, and the ability to submit or access an existing request through any desktop or mobile device. Each request is immediately acknowledged, reviewed carefully by the appropriate medical experts, with every effort made to provide a response promptly within a maximum of 5 working days once all required medical information has been provided by the treating physician. However, these timelines may be impacted by various factors, such as specific local requirements, HA, or ethics committee procedures. Requests are always assessed in consideration of applicable local laws and regulations.

In 2020, Novartis has so far received and reviewed a total of 7,620 MAP requests, including 4,434 (58%) for oncology indications (as of October 30, 2020). Requests have been received from 89 countries, and a cumulative total of nearly 14,000 patients are currently on treatment via Managed Access across all indications. **Table 1** shows our top 5 countries, compounds and indications.

ACCESS TO MEDICINES FOR COVID-19 INDICATIONS

Based on the rapid growth of Managed Access request activity for medicines to address COVID-19 received by Novartis and other pharmaceutical companies through their respective programs, we believe that a better understanding of how these channels are being used will contribute to our collective global health response to the pandemic. However, the use of these programs in the global COVID-19 response has not been widely discussed in the literature.

The Novartis Managed Access activity for COVID-19 provided specific unapproved and repurposed therapeutic products to nearly 6,000 patients over a 6-month period (i.e., from March to August 2020), including 1,500 via individual patient requests and an estimated 4,500 through institution or government requests. For context, in the first 10 months of 2020, the COVID-19-related individual patient requests represent ~ 21% of the total volume (**Table 1**). Novartis has also initiated phase III clinical trials to study the efficacy and safety of these compounds in COVID-19 indications.[6,7]

GOVERNMENT/HEALTH CARE INSTITUTION "BULK" ACCESS REQUESTS

Some countries have a channel to secure bulk quantities of a product, which is unapproved or unavailable locally and typically already licensed by at least one major regulatory authority for the specific indication of request. Novartis refers to such type of MAP requests as "Institution/Government Requests" (IGRs), as these unsolicited requests are usually placed by governments or healthcare institutions, compared with other MAP requests, which are made on an individual or "named patient" basis.

As noted above, this IGR channel has been used extensively by many countries and institutions in pandemic epicenters during 2020. To date, over 150 such requests have been approved, impacting more than 5,000 patients. For context, COVID-19-related use accounts for 77% of the total IGR requests approved by Novartis to date in 2020 and represents a 20-fold increase vs. the 2019 use of this channel. These COVID-19 IGR requests have also come from a range of countries, many of which had not initiated any Managed Access requests prior to 2020.

Given the scale of the pandemic in some countries and the urgency to initiate treatment, it is understandable that many countries opted to use this channel. The use of this "bulk access channel" is an important supplement to the individual patient request channel given the practical limitations of processing individual patient requests in a timely and effective manner—especially in light of the magnitude of the pandemic in some countries, the resulting urgency to initiate treatment and national treatment policies put in place to manage the pandemic.

RESPONSIBLE ADMINISTRATION OF MANAGED ACCESS

Embedded into all Managed Access agreements at Novartis are a range of obligations for treating physicians, institutions, and governments, which are important for the responsible provision of medicines through these access channels. These obligations include ensuring that patients are properly consented and informed of the licensure status of the therapeutic products involved, appropriate oversight and approvals by local ethics committees/institutional review boards and HAs, as well as safety reporting in alignment with local laws and regulations. We believe that collection and reporting of patient outcomes, albeit limited, should be explored to enhance the real-world evidence generation on treatments being used for COVID-19 to fight the overwhelming inflammatory reactions and prevent the

Table 1 Top five countries, compounds and indications for Managed Access patient requests in 2020 (as of October 30, 2020, total of 7,620 requests)

Countries (number of requests; % of total)	Compounds (number of requests; % of total)	Indications (number of requests; % of total)
Italy (1,157; 15%)	Alpelisib (1,605; 21%)	Coronavirus infection (1,582; 21%)
France (808; 11%)	Ruxolitinib (1,383; 18%)	Metastatic breast cancer (1,285; 17%)
United States (653; 9%)	Canakinumab (661; 9%)	Secondary progressive multiple sclerosis (399; 5%)
Canada (556; 7%)	Dabrafenib/trametinib (488; 6 %)	Graft vs. host disease (391; 5%)
Belgium (399; 5%) Australia (399; 5%)	Clofazimine (470; 6%)	Chronic myeloid leukemia (327; 4%)

emergence of cytokine storm contributing to respiratory distress in these patients.[8–10] The COVID-19 pandemic, access to and provision of therapies to address it, availability and robustness of evidence to guide decision making, and equitable allocation of treatments and resources, has raised a lot of ethical issues, which are beyond the scope of this paper but already described in the literature.[2] However, Novartis works with an independent bioethics advisory committee, consisting of expert bioethicists, healthcare professionals, and patient advocates in developing its operational and ethical guidelines, and obligations for Managed Access.[5]

NEXT STEPS AND CALL TO ACTION

Our experience to date with Managed Access showed that the complex and ever-evolving nature of the regulatory landscape warrants that we anticipate and plan for situations that may not fall within the norm. There is also a high variation in the regulations and requirements across countries. Increased visibility and transparency in our approach to Managed Access toward patients, caregivers, physicians, and healthcare professionals worldwide is essential to ensuring that more patients in need can benefit from these programs.

We will continue to monitor the COVID-19 Managed Access request activity and reflect on our full-year 2020 data once available. Of course, continuing provision of these medicines under Managed Access channels will be further informed by clinical trial results once available.

Should there be positive readouts from the ongoing phase III COVID-19 vaccine trials, Managed Access mechanisms could have utility in various countries for the vaccine distribution, enabling rapid patient access, albeit to a defined patient group(s), prior to obtaining regulatory approval.

We highly encourage other reports on similar Managed Access or compassionate use activity in response to COVID-19 indications in order to strengthen our collective understanding of how these access channels are contributing to the global health response to the pandemic.

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CONFLICT OF INTEREST

P.A. reported that he is an employee of Novartis Pharma AG and that he owns company shares. S.S. reported that she is an employee of Novartis Pharma AG and that she owns company shares. P.F. reported that she is an employee of the GE2P2 Global Foundation, which provides bioethics advisory services to Novartis Pharma AG.

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