An ethical evaluation of Conditional Marketing Authorisations

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Introduction

Since 2006 the European Medicines Agency (EMA) has been granting Conditional Marketing Authorizations (CMAs) (1). These are drugs for which research has indicated preliminary beneficial effects for diseases lacking adequate treatments. These drugs are granted CMA to get access to the European market. Further research is conducted in a clinical setting. The number of drugs that have gotten a CMA has been increasing since 2006, with 30 issued between 2006 and 2016, and 9 in 2022(1,23).

In a standard situation, the EMA gives a market authorization when comprehensive data shows a positive benefit-risk balance of a drug. For a drug to get a CMA it needs to meet four criteria. First, the drug must fulfil an unmet medical need, like a drug for a disease that has no cure. Second, the non-comprehensive evidence suggests a positive benefit-risk balance of the drug. Third, the applicant of the drug needs to prove that they will be able to provide the comprehensive data that is required to make an adequate decision by the EMA to give the drug a market authorization. Fourth, the benefit of the immediate access to the drug for patients with the unmet medical need is greater than the risk of the effect that the data is not comprehensive. This last point shows the uncertainty around the CMA, because it is not known what the exact benefit-risk balance is (1).

The use of CMAs introduces new possibilities, allowing for faster market entry of new drugs and earlier treatment options for patients with diseases which do not have treatment options. However, this situation raises several points that require careful consideration, as the research world now intersects with the clinical realm and causes a hybrid situation where there is an interest for curing a patient, but also an interest in getting the comprehensive data.

One of the problems is that a large amount of physicians have insufficient understanding of the CMAs regulatory pathway and tend to overestimate the effectiveness of the CMAs. This affects the informed consent given by these physicians to patients.

Additionally, various CMAs have been withdrawn from the market during the post-authorization research phase, revealing that these drugs were not as effective as initially thought. Although this may be a calculated risk of the pathway, the problem is that the time to withdrawal is often long, with the longest duration being 9 years. This implies that patients have been exposed to medicines with a negative benefit risk ratio during that time. Other problems are the transparency of the EMA about the CMAs, it is hard to find information about the status of the CMAs. Also there can be problems with the financial side of the CMA. We see that the coverage of the CMAs is not always assured before the trials. This can lead to an situation where the CMA will not be covered by the insurance companies.

In the literature an analysis of the ethical aspects regarding the CMAs is lacking. This paper aims to provide an overview of ethical issues related to CMA. The various ethical aspects are grouped under four headings: Uncertainty and informed consent, potential harm of the CMA procedure, the transparency of the CMAs and the financial compensation after the CMAs are granted market authorization.

Methods

For this paper multiple strategies to identify relevant literature were used. First there was a search at Google scholar and Pubmed. Keywords used were “ethics in research”, “conditional market authorization” and “uncertainty”. Also, there was contact with two experts, one in the field of ethics

and the other in the field of authorization of medication by the EMA. Both experts delivered input and provided articles related to the subject.

These two ways provided the largest amount of articles, the rest was found by snowballing through the references of the articles.(18)

Ethical Discussion Points

1. Uncertainty and Informed Consent

Informed consent, a fundamental principle in a treatment agreement, involves providing patients with comprehensive information about a drug/treatment, enabling them to make informed decisions. The importance of informed consent is reflected in laws and guidelines that govern both research and care. For example, The Nuremberg Code (19) and the Helsinki Declaration (18), which were adopted after the nazis performed extreme human research during world war two and the Belmont report (20), which was published after the Tuskegee incident where as part of an experiment Afro-Americans were not treated for their syphilis and many died. In the individual care setting, law and ethics also demand that informed consent of a patient is obtained prior to medical treatment.

In the normal situation of market authorization of medicines, the benefit-risk balance is based on comprehensive data and this reflects a certain evidence base which is considered necessary to allow doctors to prescribe the medicines to patients. In the situation of a CMA the benefit-risk balance is based on non-comprehensive data. This means there is heightened uncertainty that the health care system needs to deal with. Because there is more uncertainty regarding the effect of the CMA the informed consent is even more important. But that can only be possible if the physicians who prescribe the CMAs are aware of their status with regard to the evidence underlying the decision to grant marketing access.

There is a lack of knowledges among physicians who may not fully comprehend the uncertainty associated with CMAs, potentially leading to overly optimistic assessments. 30% of the physicians in the United States do not comprehend the uncertainty around the CMAs. The physicians don't understand that the data is not comprehensive this results in them being too optimistic. This leads to the fact that the physicians are not able to provide good informed consent which is even more important for CMAs as earlier discussed(2).

There is also a lack of knowledge among the general population, as demonstrated by a U.S. study on perceptions of FDA-approved drugs (3). 39% of the population think the FDA only approves medication which is highly effective and 25% thinks the FDA will not allow drugs with serious side effects. This shows that there is a huge gap between the knowledge of the general population, which are the potential patients and the real situation. The lack of knowledge of the physicians and the gap in knowledge of the general population, the patients, together show that it is hard to give proper informed consent. High levels of uncertainty hinder effective informed consent, impeding comprehensive understanding and hindering informed decision-making.

These uncertainties around the CMAs are difficult for patients and doctors to deal with. Medendorp et al. did research on communicating uncertainty and illustrated these difficulties. After physicians explain the uncertainties, they have to support the patients. Meaning they don't only give the message, but also help the patients with the consequences and the questions they have. It is also important to counterbalance the uncertainty with some kind of control. This is especially necessary in palliative patients because they often lack control of the situation. And because CMAs are often given to patients in a seemingly endless situation, physicians need to give them some sort of control (4).

Communicating uncertainty also depends on the situation, the patient and the physician. Patients with a lesser understanding of the CMAs and their position, might not be able to understand the information around the uncertainty, whereas emotional or anxious patients may benefit from some sort of control to counterbalance the uncertainty (4). Physicians should try to see what the patients in front of them need regarding this uncairtanty.

But what happens when patients are unrealistic optimistic? Delaney shows that it may be beneficial to be an unrealistic optimist. He states that: ”The most plausible way of understanding it is that one waives the right to be treated as if they were realistically hopeful. But note that merely being treated as though one is unrealistically optimistic does not entail that one actually is unrealistically optimistic. Being unrealistically optimistic is a matter of one’s beliefs”. The other argument is that having unrealistic optimism does not always change a patients decision (7).

Normally the EMA decides if a medicine is allowed onto the market or not. When the EMA gives a CMA, they want to wait for the comprehensive data to decide regarding allowing the CMA onto the market. But because the EMA now chooses for a third option, delaying the choice until after getting the comprehensive data, a part of the responsibility of the safety of the medicine goes to the physicians who prescribe the CMA. Physicians need to think more carefully about giving a treatment which is not approved by the EMA.

Moreover, given that CMAs often involve severe or untreatable conditions, patients facing such situations may be more inclined to embrace new drugs hoping to find a solution. For these patients, it is crucial that physicians carefully consider the drugs prescribed. Furthermore, the communication of information to these vulnerable patients must be handled with greater precision (5,6).

2. Potential harm of the CMA procedure

In recent years, several CMAs have been withdrawn due to unforeseen inefficacy, raising ethical concerns about the duration of participants' exposure to potential risks. Emanuel's 7 ethical principles underscore the importance of minimizing such exposure (10). A closer look at the duration of post-marketing research (one of the points of Emanuel) is warranted. Additionally, it is observed that certain drugs, such as Gamifant (2020) and Turalio (2020), have had their CMAs refused. This prompts consideration of the adequacy of pre-approval research in predicting a drug's effectiveness.

Questions arise concerning how participants for CMAs are recruited, whether it is limited to specific centers, and whether individuals can choose not to participate. Because we see that the time to get the comprehensive data is sometimes to long. This might be shorther when more patients are included. Additionally, ethical considerations surround the voluntariness of research participation, with others like Harris are arguing for a moral obligation to contribute to collective knowledge (8).

This is a critical point, as CMAs introduce a hybrid practice of research and clinical settings, where the interests of both patients and research must be served. The extent to which voluntariness in research participation should exist becomes a pertinent question. Harris states that it is a moral obligation to participate in clinical research. He states that: “The argument concerning the obligation to participate in research should be compelling for anyone who believes there is a moral obligation to help others, and/or a moral obligation to be just and do one’s share. Little can be said to those whose morality is so impoverished that they do not accept either of these two obligations.” Which means that if you think that you have to help others you are obligated to participate in clinical research. He does state that the research conducted needs to be with minimal risk and to be minimally invasive (8).

It is important for research to get the comprehensive data that enough patients contribute. Miller states that there is also a way to “persuade” patients to participate with the research. He states that at this moment there are two ways that insurers cover the cost of a drug. They cover the cost of the

medicine or they refuse coverage. Miller states there is another option: coverage with evidence development (9). This means that when patients participate in the research they get their drug and/or interventions covered. This will lead to more patients participating in research leading to a faster development track for the CMAs. But to coerce patients this way is against the principles of Emanuel, this show how delicate this question is and that there are two ethical principles that go against each other.

3. Transparency and Findability

The EMA website provides information on CMAs issued between 2006 and 2016; however, accessing recent data and withdrawn CMAs proves challenging, there is no overview of all the current CMAs and also it is hard to find if and why CMAs are revoked and/or revoked. Transparency is vital for evaluating the CMA approval process and for understanding outcomes. A clear overview of all issued and withdrawn CMAs is essential for accountability (11).

The transparency of the EMA can have consequences for the trust of the general population in the EMA. As discussed earlier, the general population may think that only very effective medicines without serious side effect are allowed into the market (17). It could be possible that when the an overview of the CMAs is given this could have an impact on the thoughts of the general population about the EMA/ FDA and their credibility.

4. Introducing 'Research' into 'Clinical Practice'

CMAs serve as an initial step in integrating research into clinical practice, creating a continuous process of evaluating drug's effectiveness and risks. To achieve this, Faden identifies seven prerequisites, including respecting patient rights, acknowledging clinical judgments, ensuring optimal patient care, avoiding non-clinical risks, addressing inequality, conducting continuous research for clinical care improvement, and fostering patient collaboration for the common good (12).

In conclusion, the evolving landscape of CMAs necessitates thorough examination and thoughtful consideration of the ethical, procedural, and communicative challenges they present at the intersection of research and clinical practice. Balancing the interests of patients and the imperative to advance medical knowledge requires ongoing reflection and adaptation of regulatory frameworks.

5. Compensation for CMAs

When a new drug comes into the European market there is an agreement about the prices to be paid. This agreement is partially based on the effectiveness of the medicine. Because there is uncertainty about the effectiveness not all CMAs have an agreement on the price(22).

In the research stage of CMAs all costs are covered because the CMAs are in a research stage. When the CMAs are allowed onto the market the finance structure will be different and should be covered by insurance companies. There is already discussion about cost-effectiveness. This could lead to the situation that a CMA is proven effective and allowed onto the market. If after the CMA is approved the cost-effectiveness of the CMA is not positive it is possible that the CMA won't be covered.

Sandman discussed that with the CMAs we are going from an evidenced-based to a hope-based system, where the cost-effectiveness of CMAs is not positive (13). He thinks that the costs of CMAs are higher that the benefits. This is also because the financial side is not taken into account before conducting all the studies to collect the comprehensive data.

Conclusion and Discussion

This article has attempted to systematically review the ethical aspects of CMAs. The introduction of CMAs is positive because of the fact that it provides earlier access to patients with unmet medical needs. Which will help these patients and can also give hope to them.

But this article also shows that physicians who prescribe CMAs don't always know what the status of CMA means and what the expected benefits are of the CMAs. That is one of the reasons to be careful with the CMAs because they come with uncertainty which raises ethical dilemmas. It is important that our healthcare system and the physicians know about the CMA and their status, so that they can address the uncertainty and they need to learn how to communicate that uncertainty with the patients.

When the physicians know the status of the CMAs and what the expected benefits are tot the health of the patients they can give better advise to the patients. But there is more uncertainty in CMAs and patients might be unrealistic optimistic about the effects of the CMA but as discussed earlier Delaney notices that unrealistic optimism might not be problematic(7). As long as patients are well informed, unrealistic optimism is not always problematic.

Furthermore we noticed that some trials of CMAs take longer than can be expected. It is important that the CMAs will provide the comprehensive data in a certain amount of time. It is important for the EMA but also the medical manufacturers that the time needed to provide this data will be reduced. One of the problems with the duration of the research is patient involvement. There is a need for enough patients to provide the comprehensive data. As discussed earlier there is a ethical dilemma. On the one hand we want research to be voluntary, like Emanuel says (10). On the other hand people like Miller say that with obligations for patients who get CMAs the results of research will be earlier available, helping the general population. Although these obligations to participate in the research should be as little as possible. This shows the ethical dilemma on (voluntary) participating in research.

In the research of this article it was hard to get access to all the information about different CMAs. It is important that the EMA will provides easier access to the data about the CMAs and will be more transparent. This will ensure that other parties can control the EMA and see what the effects are to ensure patient safety.

In the current system we see that before a CMA is granted the coverage of the CMA is not provided. Which can lead to the situation when the CMA grants access to the market the CMA is not covered by the insurance companies. It could be better if the financial side of the CMAs would be included before granting the CMA. Otherwise it would be a waste of resources and because it would be problematic if the CMA would increase the inequality in access to medication.

This is the first study that tries to systematically evaluate the ethical part of the CMAs. There are more papers about the ethics concerning CMAs, but none of the papers we found were about the ethics in a broader view.

In conclusion, CMAs contribute to a better healthcare system. By providing earlier access for patients with unmet medical needs. But we need to optimize the conditions so that the safety of these patients is secured and the risk are minimalized. This can be done by educating physicians about the status of CMAs and their effectivity. And also the process of getting the comprehensive data needs to be more efficient so that patients will not be exposed to more risks than necessary. More research should be conducted to improve the learning healthcare system, while make the risk for patients as low as possible.

Bronnen

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