April 5, 2023

Expert Committee on the Selection and Use of Essential Medicines World Health Organization, Geneva

Re: Arguments against the application for the inclusion of fentanyl citrate for breakthrough cancer pain in the Model List of Essential Medicines

Dear Members of the Committee,

Pallium India is a non-profit organization with a vision to integrate palliative care with mainstream healthcare. Its flagship clinical program- Trivandrum Institute of Palliative Sciences (TIPS) – is a WHO Collaborating Centre for Training and Policy on Access to Pain Relief. Pallium India has Consultative Status (Special) with the UN Economic and Social Council (ECOSOC).

Pallium India has actively participated at the international level in guideline development groups, technical meetings, projects and programs related to the safe and rational use of essential medicines, including internationally controlled substances.

We write to you to strongly oppose the application for inclusion in the WHO Essential Medicines List of fast-acting oral fentanyl for treatment of breakthrough pain in cancer patients. Below are the reasons why:

- We would underscore the point that the WHO EML already includes immediate release morphine and is the strong opioid of choice for treatment of moderate to severe pain recommended by the WHO. However, it remains inaccessible to most people living in Low- and Middle-Income Countries because of multi-level barriers.
- Fentanyl is 150 times more expensive that immediate release oral morphine, and inclusion of such an expensive opioid as an essential medicine for breakthrough cancer pain is unjustifiable because it would cause financial destruction of whole families in the low-and-middle income world which forms 84% of the global population.
- Our colleagues at the International Association for Hospice and Palliative Care (IAHPC) have submitted a detailed letter also opposing this, wherein they have listed several issues and concerns ranging from the pharmacokinetic properties, issues around inadequate training of professionals in its use, as well as the risk of further complicating already complex regulatory issues around the safe use of opioids for pain relief.

In addition: No evidence exists to support the need for, or the addition of, another pure agonist to treat breakthrough pain. The application lacks data on dose-equivalence for transmucosal fentanyl compared to other opioids and oral, modified-release formulation of fentanyl. This means using transmucosal fentanyl to commence or titrate opioids to effect is less safe than the usual, recommended practice of immediate- and modified-release morphine (or equivalent opioids).

The application refers to a study comparing the cost of transmucosal fentanyl citrate with intranasal fentanyl preparations. This cannot be verified as the study is not included in the references.

For the reasons stated above, Pallium India strongly recommends the use of generic morphine with immediate release and sustained release oral preparations for pain management. Breakthrough pain is not homogenous and whilst transmucosal fentanyl has a place in some types of breakthrough pain and

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for some patients, it does not and must not replace immediate-release morphine.

The WHO has expressed its commitment to improving access to morphine as a part of Primary Health Care and Universal Health Coverage. This important objective aligns with a series of resolutions from the World Health Assembly, including WHA67.19 *Strengthening palliative care as a component of comprehensive care throughout the life course* and WHA67.22 *Access to essential medicines*.

In essence, the inclusion of this formulation of fentanyl does not reflect the spirit of the WHO Model List of Essential Medicines and does not meet the criteria for its inclusion: In regards to "disease prevalence", given it is applicable only to a very specific group; in regards to "evidence on efficacy and safety", given the high risk of misuse and insufficient evidence supporting its superiority to morphine; and in regards to "comparative cost- effectiveness", given that the cost outweighs the benefits regarding immediate-release morphine. In addition to the non-beneficence of the inclusion, it may harm already weak and poor health systems in Low- and Middle- Income Countries.

Governments should ensure that immediate release oral morphine is always available in public healthcare institutions before other more expensive opioid formulations become available. Where more expensive or injectable opioid formulations are already available and immediate release oral morphine is not, they should take immediate steps to ensure that it becomes available.

Rather than introducing a new formulation to the WHO EML, efforts should be made to improve the supply chain of generic, inexpensive morphine, provide educational training to healthcare professionals, and create balanced policies for the safe, rational use of controlled medicines for the millions of people who still live and die in pain due to limited or no availability.

Respectfully submitted.

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