

## Grounds for Opposing Patent Application for Bedaquiline Formulation in India

In an effort to make lifesaving drugs accessible to all people, civil society organisations around the world have worked tirelessly to remove patent barriers on drugs for the treatment of cancer, HIV and hepatitis C. In India, the largest manufacturer of affordable drugs for the developing world, the struggle to scale up access to medicines for drug-resistant tuberculosis (DR-TB) is now at a decisive stage. Médecins Sans Frontières (MSF) and civil society organisations in the country are supporting a patent challenge filed by two TB survivors in order to prevent pharmaceutical corporation Johnson & Johnson (J&J) from extending its monopoly on the core DR-TB drug bedaquiline.

### Background

In August 2018, the World Health Organization (WHO) announced an update to its treatment guidelines for multidrug- and rifampicin-resistant TB (MDR/RR-TB) to include the use of bedaquiline as a core drug in standard treatment regimens for MDR-TB, highlighting “the immediate steps to be taken to ensure that MDR/RR-TB patients receive treatment in accordance with the latest evidence on effectiveness and safety.”<sup>1</sup> The updated treatment guidelines prioritise the use of bedaquiline as a drug with the lowest risk of serious side effects. The guidelines now include bedaquiline as a highest-ranked option (Group A) and recommend limiting the use of injectable aminoglycosides (included in Group C, the least preferred option).<sup>2</sup>

In July 2018, South Africa’s DR-TB directorate acknowledged improved cure rates and a significant reduction in mortality among patients treated with bedaquiline and recommended that access to the drug be provided to all patients diagnosed with any form of drug-resistant TB (RR-TB, MDR-TB, pre-extensively drug-resistant TB [pre-XDR-TB], or XDR-TB).<sup>3</sup>

According to the updated WHO guidance, bedaquiline-based treatments are now recommended for a larger number of people, which, in turn, calls for national TB programmes to immediately increase access to bedaquiline-containing regimens. Positive results from studies currently underway on the use of bedaquiline in all-oral, shorter-course regimens could result in even greater potential patient benefit and wider use of bedaquiline in TB programmes globally.

To date, only 25,000 people worldwide have received bedaquiline, nearly 70 per cent of whom have been treated in South Africa.<sup>4</sup> Increasing the number of affordable sources of bedaquiline is critical to lowering prices for the lifesaving drug and ensuring that people in desperate need can access it in other TB high-burden countries. However, patent barriers threaten to continue blocking the introduction of alternative suppliers. To save lives, these patent barriers must be urgently and effectively addressed.

### Patent situation in India

In India, a majority of pharmaceutical patents are filed for secondary claims, i.e., for marginal improvements on patented drugs that already exist and should not be granted protection again. Such ‘evergreening’ tactics allow pharmaceutical corporations to maintain exorbitant drug prices by extending their monopoly on the market and delaying the introduction of alternative sources of drugs. This is concerning because it blocks Indian generics manufacturers from producing lower-priced generic versions of drugs – including child-friendly formulations – despite their technical capacity to do so.

Janssen Pharmaceutica N.V. (Janssen), a subsidiary of the pharmaceutical corporation J&J, has filed for multiple patents on bedaquiline in India, not limiting itself to the basic compound patent but also filing secondary patents to stake claims on routine improvements and formulations. Currently, Janssen exerts control over the market until 2023, when its compound patent is set to expire. Should it be granted, a secondary patent

on the fumarate salt of bedaquiline will further delay the entry of alternative suppliers to the market until the end of 2027.

<b>WO Publication Number/ Coverage</b>	<b>India Patent Application Number/Patent Number</b>	<b>India Status/ Expiry Date</b>
WO2004011436 Bedaquiline base compound, its salts, isomers and enantiomers	220/DELNP/2005 Granted as: IN236811	Granted 18 July 2023
WO2008068231 Pharmaceutical compositions/ formulations of bedaquiline fumarate and a wetting agent	1220/MUMNP/2009	Under examination 3 December 2027 (if granted)

While the barrier to competition created by the bedaquiline base compound patent can be effectively addressed through a compulsory license (and civil society in India has written to the government on the matter<sup>5</sup>), it is crucial that the Indian Patent Office rejects the secondary patent claim, currently pending, as per the provisions of the Indian Patents Act. According to Section 25 (1) of the Indian Patents Act, a pre-grant opposition can be filed at any time and by any person until the grant of the patent. The pre-grant opposition is then taken up for hearing and a detailed order is passed by the Controller of Patents.

A recent study on the Indian Patent Office has highlighted that a significant proportion of patents – over 70 per cent of those granted from 2009 to 2016 – are for marginal improvements, many of which have been granted despite the anti-evergreening provisions in the Indian Patents Act, which restricts the patentability of a host of secondary claims.<sup>6</sup> This lack of rigorous assessment of the patent eligibility of pharmaceuticals is worrisome because it acts as a direct barrier for access to lifesaving medicines for people in need.

Patent oppositions to Janssen’s bedaquiline formulation are vital to preventing additional unmerited patents from being granted. If the opposition is successful and the patent is denied, when the basic compound patent expires in India alternative suppliers will be able to enter not only the Indian market but also export this crucial medicine to other countries.

## **Development of bedaquiline was a collective effort and access to the medicine should reflect this**

The rationale for granting monopoly rights on new medicines is allegedly to protect the patent holder’s investment and encourage them to invest further in research and development of new medicines. However, patents permit pharmaceutical corporations to charge high prices in the absence of competition. Moreover, pharmaceutical corporations charge high prices despite benefitting substantially from public funding for drug research.

The history of bedaquiline’s development reflects a genuinely collective effort. As such, Janssen should not be allowed to extend its monopoly on bedaquiline through evergreening strategies in India or in other countries.

The US Food and Drug Administration (USFDA) first gave accelerated approval to bedaquiline based on phase IIb data, out of desperate need for new and improved treatments for MDR-TB, since success rates using available treatments remained abysmally low. Several of the phase I and II trials conducted prior to the drug’s registration were sponsored by public and philanthropic organisations such as the US National Institutes of Health/National Institute of Allergy and Infectious Diseases<sup>7</sup> and the TB Alliance.<sup>8,9</sup>

J&J did not invest directly in phase III trials as part of their initial bedaquiline development programme. Several research institutes and treatment providers, including national TB programmes and MSF, have invested in additional trials, operational research, and pharmacovigilance to document the safety, efficacy and optimal use of bedaquiline for the treatment of MDR-TB. A phase III trial (STREAM II) is currently

underway, sponsored by the International Union against Tuberculosis and Lung Disease and funded by USAID.<sup>10</sup> With funding from Unitaid, MSF in collaboration with Partners in Health are also conducting a phase III clinical trial that includes bedaquiline.<sup>11</sup>

J&J has also already received significant financial compensation for the development of bedaquiline. The drug was granted orphan drug designation by the USFDA, which provided the pharmaceutical corporation with a 50 per cent tax credit on qualifying clinical research and development expenditure. It also received a tropical disease priority review voucher, which the company used to accelerate review and marketing authorisation of another drug in their portfolio – guselkumab, a blockbuster psoriasis drug. This drug sells for nearly US\$60,000 per patient per year in the US and is estimated to yield US\$3.49 billion in sales by 2024.<sup>12</sup>

These public contributions warrant a common right to use that should ensure that bedaquiline is accessible to all TB patients who need it and to TB programmes worldwide, especially in TB high-burden countries. J&J's secondary patent application blatantly disregards public contributions to the development of the drug, and thus the secondary patent claim should be unequivocally rejected.

In September 2018, MSF sent an open letter to J&J urging the pharmaceutical corporation to take action so that countries can access an affordable and sustainable supply of bedaquiline for the treatment of MDR-TB.<sup>13</sup>

## **In-depth: Grounds for opposition to bedaquiline fumarate salt patent application**

Indian Patent application no. 1220/MUMNP/2009, titled “FUMARATE SALT OF (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO) ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL”, was initially focused on a fumarate salt of bedaquiline.

However, when the Network of Maharashtra People Living with HIV (NMP+) filed a pre-grant opposition in 2013 and the Indian Patent Office raised objections, Janssen modified its claims to cover a composition of bedaquiline fumarate and a wetting agent. If granted, the patent would continue to operate until December 2027, ensuring Janssen's patent monopoly for bedaquiline in India beyond July 2023 (when the bedaquiline base compound patent in India will expire).

The current opposition is filed by Nandita Venkatesan, from Mumbai, India and Phumeza Tisile, from Khayelitsha, South Africa, both of whom survived DR-TB but lost their hearing because of the toxicity of the treatment. The opposition is based on grounds of lack of novelty, lack of inventive step, lack of enhanced therapeutic efficacy, and for the formulation being a mere admixture.

- **Novelty:** Patents should not be granted on claims of ‘invention’ that have been disclosed in a published document before the date of filing of the patent application of the claimed invention. The patent granted to Janssen, namely IN236811, already discloses the bedaquiline free-base compound and its additional salts, including fumarate salts and surfactant (wetting agent). Thus, the invention being claimed in patent application no. 1220/MUMNP/2009 has already been disclosed in Janssen's earlier patent.
- **Inventive step:** Patents should not be granted on compounds that would have been obvious to make or arrive at based on existing knowledge or well-known techniques. Janssen's patent on the bedaquiline free base compound, Janssen's earlier patent on rilpivirine, and other literature have demonstrated that making a salt form of a known compound – in this case, bedaquiline – is obvious and cannot be termed as inventive. Shockingly, Janssen's claims are a verbatim copy of its earlier patent application on rilpivirine, which was rightly rejected by the Indian Patent Office.<sup>14</sup>

Rilpivirine Application	Bedaquiline Salt Application
<p>[Page no. 9, Para no. 077]</p> <p>“Solid pharmaceutical compositions according to the present invention may comprise by weight based on the total weight of the composition:</p> <p>(a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);</p> <p>(b) from 0.01 to 5% of a wetting agent;</p> <p>(c) from 40 to 92% of a diluent;</p> <p>(d) from 0.1 to 5% of a glidant.”</p>	<p>[Claim no. 3]</p> <p>“3. A pharmaceutical composition according to any one of claims 6 to 10 comprising by weight based on the total weight of the composition:</p> <p>(a) from 5 to 50% of active ingredient;</p> <p>(b) from 0.01 to 5% of a wetting agent;</p> <p>(c) from 40 to 92% of a diluent;</p> <p>(d) from 0.1 to 5% of a glidant.”</p>

- **Efficacy:** India’s Patents Act stipulates that in order to be granted a patent, new forms of known substances have to demonstrate that they have enhanced the therapeutic efficacy of the known product. This requirement (included in Section 3(d) of the Patents Act) was designed to clamp down on evergreening. The knowledge of the efficacy and existence of the bedaquiline base compound predates the date of filing of the patent application, and thus Janssen’s present patent application that covers a formulation of bedaquiline fumarate salt and a wetting agent is invalid. Janssen has not provided any evidence in its application to demonstrate enhanced therapeutic efficacy of the allegedly new formulation of bedaquiline over its previously known form. Such disclosure is required and has been stipulated by the Supreme Court of India in its decision in Novartis AG vs. Union of India, 2013.<sup>15</sup>
- **Mere admixture:** In case a patent is claimed over a combination of substances, Section 3(e) of India’s Patents Act requires the patent applicant to show that the combination being claimed as an invention has additional or synergistic results and that the combination is not just a mere aggregation of qualities of the substances forming the combination. Janssen’s present application does not disclose any data on a synergistic effect resulting from the combination of known compounds, i.e., bedaquiline and the wetting agent.

This is a classic case of evergreening so as to extend the monopoly of the drug in the market. When faced with a drug with low bioavailability, the widely-adopted strategy is to make a fumarate salt of such drug, add a wetting agent to finally make a composition of such fumarate salt and thus seek another patent that will extend monopoly control over the drug.

For the reasons outlined above, the patent application should be rejected as it does not meet the patent eligibility standards under the Indian Patents Act, 1970.

**To read the opposition in detail, see:**

[https://www.patentoppositions.org/en/drugs/bedaquiline/patent\\_oppositions/5c5c0b4bd2708f0005c98d08](https://www.patentoppositions.org/en/drugs/bedaquiline/patent_oppositions/5c5c0b4bd2708f0005c98d08)

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