



**A OVERVIEW ON BEDAQUILINE FOR THE TREATMENT OF DRUG-
RESISTANT TUBERCULOSIS****P. SIVARAM KUMAR^{*}, M. ARAVIND, M. VENKATA RAMANA, RAMARAO N**Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi
Nagar, Lam, Guntur-522034***Corresponding Author: Mr. P.Sivaram Kumar: E Mail: sivacomputer91@gmail.com**Received 26th Nov. 2020; Revised 30th Dec. 2020; Accepted 11th Jan. 2021; Available online 1st Oct. 2021<https://doi.org/10.31032/IJBPA S/2021/10.10.5662>**ABSTRACT**

Bedaquiline has been recently approved drug moiety for the treatment of pneumonic multidrug-safe tuberculosis (TB) as a component of mixed treatment in adults. Existing medicines for multi-drug safe tuberculosis (MDR-TB) have significant limitations, to the extent of their feasibility, result profile, and unconventionality of association. Bedaquiline is a novel diarylquinoline against microbial that has starting late been investigated as an assistant to existing medicines for MDR-TB. In this review, the overall properties of bedaquiline were consolidated like physicochemical properties, dose administration, mechanism of action, pharmacokinetics, pharmacodynamics, drug interactions, and side effects for better understanding.

Keywords: bedaquiline, diarylquinoline, multidrug resistance, Mycobacterium tuberculosis, tuberculosis

INTRODUCTION

Tuberculosis (TB) is contagious bacterial contamination due to mycobacterial species of the MTB complicated, maximum frequently mycobacterium tuberculosis. It's miles predominantly an airborne ailment, spread through individuals with energetic TB, that commonly impacts the lungs,

however, can spread to other organs. globally, TB is a sizable public fitness issue. In 2011, an anticipated 1.7 million people died from TB. about one in three individuals international is latently inflamed with *m. tuberculosis*, and 10% of those infected will finally broaden the

active ailment. HIV-high quality individuals are a specifically inclined populace, with a lifetime risk of developing energetic TB of fifty%—5 times extra than that of HIV-terrible people [1].

The effective remedy of tuberculosis (TB) is reliant on several bactericidal and sterilizing capsules administered in combination for an ok period, to assure antimicrobial efficacy even as preventing selection of drug-resistant mutants and achieve everlasting treatment [2].

Notwithstanding progress in standard tuberculosis (TB) control over the past years, TB remains a worldwide public fitness chance. Its control nonetheless poses a prime undertaking at worldwide, countrywide and network tiers. specifically, the treatment of drug-resistant TB is of an ongoing subject, as get right of entry to diagnostic and remedy infrastructure (drug sensitivity testing, 2nd- or 1/3-line tablets and respective clinical understanding) remains limited in many countries [3]. The trendy WHOTB file predicted the incidence of all kinds of TB to be 9.zero million instances in 2013; 1.5 million sufferers died from the disorder, of which 360,000 people have been HIV co-inflamed. in 2013, multidrug-resistant TB (MDR-TB) become estimated to have newly evolved in 480,000 cases; an envisioned 210,000 (forty-three .eight%) died of MDR-TB. in 2013, globally, about 3.5% of newly

recognized TB instances and 20.5% of these formerly dealt with for TB had MDR-TB and approximately 9.zero% of MDR-TB instances in international locations with representative surveillance facts had substantially drug-resistant TB (XDR-TB). of an alarming subject, but very limited volume until the date is the emergence of sufferers with resistance past XDR-TB. tuberculosis (TB), resulting from mycobacterium tuberculosis (Mtb) [4], is the main infectious sickness killer global and consequently a major global health difficulty. One of the contributing factors to this ongoing fitness disaster is the alarming upward thrust of drug resistance. unluckily, the occurrence of drug-resistant TB has been predicted to keep rising to fight drug-resistant TB, the anti-TB drug bedaquiline (BDQ) changed into speedy-tracked for approval by the US food and drug administration (FDA) in 2012. this drug is conditionally administered for the treatment of multi-drug-resistant TB (MDR-TB), which is defined as resistance in opposition to the primary-line capsules isoniazid and rifampicin [4].

The often overdue detection of tuberculosis (TB), coupled with the want to use lengthy and complex multi-drug remedy regimens, has caused an alarming growth in cases that might be resistant to the standard front-line tablets (multi-drug-resistant; MDR). in 2016, approximately 580,000 new instances

(3.9% of latest instances and 21% of recurrent cases) were classified globally as MDR-TB, and this share has been rising rapidly [5].

BEDAQUILINE

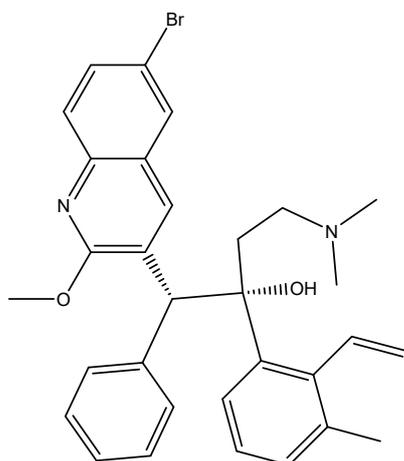


Figure 1: Structure of bedaquiline

Bedaquiline is the primary of a new class of antimycobacterial drugs with a novel mechanism of action regarding particular inhibition of mycobacterial ATP synthase. It well-known shows excessive *in vitro* interest against *M. tuberculosis* isolates which might be inclined or proof against presently available first-line and 2d-line pills and have been shown in clinical research to be energetic in opposition to drug-prone TB and MDR-TB. Bedaquiline become currently approved by the FDA and EMA for treatment of pulmonary MDR-TB as a part of combination therapy in adults when a powerful treatment regimen cannot otherwise be furnished. This evaluation summarizes the pharmacokinetic profile of

bedaquiline as well as the consequences of drug-drug interplay studies [6].

Bedaquiline is a diarylquinoline that selectively inhibits bacterial adenosine triphosphatase, which is a novel antimycobacterial goal. Bedaquiline received expanded approval within the European Union and US of America in 2012. At the time of approval, it becomes the primary antituberculosis drug from a novel class in extra than forty years. Bedaquiline is a collection of a drug (should be blanketed in all regimens) in the 2019 global health enterprise (WHO) recommended regimens for long multidrug-resistant tuberculosis (MDR-TB, defined as proof against each rifampicin and isoniazid) regimens [7]. This review describes bedaquiline destructive results, with a focal point on QT prolongation and liver injury, in addition to the effect of bedaquiline on mortality [8].

Chemical and physical properties of bedaquiline

Bedaquiline (molecular weight 555.50 Da) is a diarylquinoline with a quinolinic central heterocyclic nucleus with alcohol and amine aspect chains that might be answerable for the compound's antimycobacterial activity (determine 1). Bedaquiline is an enantiopure compound with two chiral centers (1*R*,2*S* isomer). It's miles isolated from a mixture of four isomers and is the most active stereoisomer

towards numerous lines of mycobacteria [1].

Bedaquiline is administered orally and exerts its pharmacological pastime via mainly inhibiting mycobacterial ATP synthase. Importantly, bedaquiline possesses a selectivity index of >20 000 for mycobacterial ATP synthase versus eukaryotic mitochondrial ATP synthase [9]. consequently, it isn't expected to have interaction with human ATP synthase [10].

DOSING AND ADMINISTRATION

Bedaquiline is presently available as an oral, uncoated, immediate-release pill that incorporates 100 mg of the bedaquiline-free base [11]. The advocated dose, as part of mixture therapy for pulmonary MDR-TB, is 400 mg daily for 2 weeks, accompanied by two hundred mg 3 instances according to week. regimens utilized in posted research have given the drug as part of MDR-TB therapy for as much as 24 weeks in total [12].

Mechanism of action:

Bedaquiline is bactericidal and killing is attention dependent. bedaquiline distributes substantially in tissues and binds substantially (>99%) to plasma proteins. bedaquiline has a completely lengthy terminal 1/2-lifestyles of approximately five months [13]. The most important route of metabolism is thru the cytochrome p450 (CYP) isoenzyme 3a4, which catalyzes N-demethylation to form the M2 metabolite.

M2 has a half-existence similar to the figure drug. M2 is less lively towards mycobacteria than the parent drug, however, induces phospholipidosis, which isn't necessarily toxic, and is implicated in prolongation of the QT program languageperiod. bedaquiline can be the victim of drug-drug interactions while co-administered with inducers or inhibitors of cyp3a4. bedaquiline negative reactions can be extended and/ or arise after dosing cessation, because of the very long half-life of each the determined drug and M2 [14].

List of values: Bedaquiline Plasma Pharmacokinetic Parameters for Oral 25-, 100-, and 400-mg Daily Doses for 7 Days in Humans [15].

Daily Dose:	25 mg
	100 mg
	400 mg
C_{\max} ($\mu\text{g/mL}$) :	0.32 ± 0.09
	1.21 ± 0.39
	5.50 ± 2.96
t_{\max} (h) :	3.93 (2.00-6.17)
	4 (1.97-8.00)
	4 (2.05-6.02)
AUC_{0-24} ($\mu\text{g h/mL}$) :	3.97 ± 1.29
	16.05 ± 5.07
	64.75 ± 20.7
Effective $t_{1/2}$ (hours)	24
	24
	24

Abbreviations: C_{\max} , maximum concentration; t_{\max} , time to C_{\max} ; AUC_{0-24} , area under the concentration-time curve from 0 to 24 hours; $t_{1/2}$, elimination half-life.

Pharmacokinetics:

Plasma pharmacokinetic parameters for bedaquiline administered orally are indexed in the listing of values the maximum plasma concentrations (C_{\max}) and the area beneath the plasma concentration-time curve (AUC) expanded proportionally with multiplied doses of bedaquiline, which displays a linear pharmacokinetic profile as much as doses of 700 mg. the relative bioavailability of bedaquiline will increase by using about 2-fold with the management of a well-known meal containing approximately 22 g of fat compared with management on an empty belly. plasma concentrations have been not suffering from bodyweight, with information available most effective for sufferers with a body mass index of 14.1 to 26.9 kg/m². the plasma protein binding of bedaquiline is higher than 99.9%. the quantity of distribution within the central compartment is envisioned to be approximately 164 l. in a murine model of TB, bedaquiline and its N-monodesmethyl metabolite (M2) have been substantially dispensed in the lungs, with AUC_{168h} lung/plasma ratios of approximately 20 for bedaquiline and one hundred to 2 hundred for its metabolite

[16]. Bedaquiline is metabolized through cyp3a4 of the cytochrome p450 machine and is in general oxidized to its energetic M2, which has a 4- to 6-fold decrease in antimycobacterial efficiency and decrease common publicity (23% to 31%) than the parent drug. bedaquiline is typically removed within the feces. less than 0.001% of the administered dose is removed unchanged within the urine. After reaching C_{\max} , bedaquiline concentrations decline triexponentially with time. This affords a reason for much less-common dosing regimens and for combining bedaquiline with other capsules with lengthy half-lives.25 the mean terminal removal 1/2-life ($t_{1/2}$) of bedaquiline and M2 is approximately 5.5 months and is independent of the administered dose [12]. bedaquiline is generally removed inside the feces. much less than zero.001% of the administered dose is eliminated unchanged inside the urine. after achieving C_{\max} , bedaquiline concentrations decline triexponentially with time [17]. This provides a reason for less-common dosing regimens and for combining bedaquiline with other drugs with long half-lives [18]. The imply terminal removal 1/2-lifestyles ($t_{1/2}$) of bedaquiline and M2 is about five.5 months and is unbiased of the administered dose. this prolonged removal probably displays the sluggish release of bedaquiline and M2 from peripheral

tissues, which may additionally accumulate and cause phospholipidosis [19].

Pharmacodynamics:

The exact pharmacokinetic-pharmacodynamic parameter that excellent correlates with bedaquiline has now not been properly elucidated. but, current studies have shown that AUC is the number one hobby driving force of bedaquiline [20] in a study have a look at early bactericidal pastime (EBA) in treatment-naïve patients with smear-advantageous TB, oral bedaquiline at doses of 25, a hundred, and 400 mg had nearly no bactericidal interest at some stage in days 2 to four of remedy.this could correlate with the interruption of cellular electricity hemostasis. bedaquiline confirmed bactericidal pastime between days 4 to 7, with an average lower in mycobacterial colony counts of handiest zero.77 log₁₀ colony-forming gadgets (CFU). Those outcomes are showed by a phase 2 have a look at, wherein the lower of mycobacterial CFU of bedaquiline 400 mg orally became zero.57 log₁₀ as much as 7 days of remedy. The drug's bactericidal activity was progressed between weeks 1 and 4 suggesting a time-structured killing. in assessment, the EBA of bedaquiline is regarded to grow with doses as much as four hundred mg every day and changed into set up following 2 loading doses and given for 14 days even at a low dose of one hundred mg each day. due to the

bactericidal activity of bedaquiline against dormant or nonreplicating bacilli has the capacity of shortening the period of remedy. in a murine model of TB, bedaquiline verified a greater bactericidal hobby intracellularly inside the peritoneal macrophage than at the extracellular bacilli due to the fact the preliminary static section became shorter or absent. in any other murine version, bedaquiline turned shown to possess giant sterilizing activity, and the substitution of bedaquiline for isoniazid or its addition to the standard anti-TB regimen allowed for a discount of the treatment duration to 4 months. bedaquiline displayed a synergistic effect with pyrazinamide-containing regimens in clearing bacterial counts in the lungs of mice after the handiest 2 months of therapy. The 14-day EBA of bedaquiline became additionally pronounced in treatment-naïve patients with drug-susceptible straight forward TB. M2 is not thought to make contributions significantly to clinical efficacy however seems to correlate with QT prolongation.

Drug interactions:

Bedaquiline multiplied publicity to each isoniazid and pyrazinamide. furthermore, the management of bedaquiline in association with clofazimine and moxifloxacin can also grow the chance of cardiotoxicity. For this reason, it's far wise to reveal patients for cardiac dysrhythmia

or qt prolongation, liver dysfunction, and renal impairment [21].

In step with the world fitness corporation interim coverage guidance, caution must be exercised while administering bedaquiline collectively with capsules performing on the enzyme cyp3a4 which could inhibit liver feature (i.e., ketoconazole and lopinavir/ritonavir) because they may grow bedaquiline concentrations, ensuing in toxicity or inducing liver function (i.e., rifampin), because the co-administration should result in subtherapeutic bedaquiline concentrations with decreased efficacy [21].

Svensson *et al.* stated an expanded clearance of bedaquiline when co-administered with rifampin and rifapentine. accordingly, the affiliation between rifampin, in trendy, and bedaquiline is in standard now not encouraged [22].

Adverse effects

Inside the pooled institution of subjects handled with bedaquiline on my own, as were pronounced in 60. Three% of subjects and maximum regularly related to the machine organ instructions of the anxious system (24.3%) and gastrointestinal disorders (sixteen.9%). inside these classes, the maximum common ae became headache (18.zero%). nausea, arthralgia, hemoptysis, chest pain, anorexia, and rash are different not unusual facet consequences (so as of descending

frequency) suggested all through the therapy with bedaquiline. This drug can also impact the elevation of hepatic transaminases.

The most critical facet impact that should be taken into specific account is QT prolongation. *In vitro* studies have demonstrated that cellular phospholipidosis induction, which's stronger in M2 than in bedaquiline, is liable for the development of destructive consequences together with QT prolongation, hepatotoxicity, and myopathy. however, the concentrations of M2 and bedaquiline received in invivo research did no longer produce such adverse consequences, even at the most clearance stage [22].

ADVANTAGE

Bedaquiline has been delivered explicitly to treat TB patients with microorganisms that are impervious to rifampicin just as to isoniazid, another center enemy of TB medication, and hence experience the ill effects of multidrug-safe tuberculosis (MDR-TB).

DISADVANTAGE

In addition to these obvious assets of bedaquiline, the potential disadvantages of bedaquiline include inhibition of the hERG (human Ether-à-go-related gene; KCNH2) potassium channel (concurrent risk of cardiac toxicity), hepatic toxicity, and possibly phospholipidosis.

CONCLUSION

Bedaquiline, is a first-in-class diarylquinoline, was demonstrated to be viable in blend with different specialists for the treatment of grown-ups with aspiratory MDR-TB. The oddity of the medication is in its extraordinary component of activity, wherein it hinders the proton siphon action of ATP synthase in *M. tuberculosis*. As highlighted here, bedaquiline seems to be a very promising new anti-TB drug. The potential cardiologic side effects and the reportedly linked mysterious deaths raise some concern, but the context in which these drugs would be considered is so severe that it is probably ethically worthwhile to use them. However, specific studies performed in the pediatric population are needed to confirm the PK and pharmacodynamic data in the first years of life as well as their safety and efficacy. This seems particularly important, considering the long duration of TB treatment required for MDR and XDR-TB as well as the potential interactions with other drugs included in anti-TB regimens or administered for underlying comorbidity.

REFERENCES

[1] Van Heeswijk Rpg, Dannemann B, Hoetelmans Rmw. Bedaquiline: A Review Of Human Pharmacokinetics And Drug-Drug Interactions. *J Antimicrob Chemother.* 69(9), 2014, 2310–8.

- [2] Tiberi S, Muñoz-Torrico M, Duarte R, Dalcolmo M, D’ambrosio L, Migliori Gb. New Drugs And Perspectives For New Anti-Tuberculosis Regimens. *Rev Port Pneumol (English Ed.* 24(2), 2014, 86–98.
- [3] Kakkar Ak, Dahiya N. Bedaquiline For The Treatment Of Resistant Tuberculosis: Promises And Pitfalls. *Tuberculosis [Internet].* 2014; 94(4): 357–62. Available From: [Http://Dx.Doi.Org/10.1016/J.Tube.04](http://dx.doi.org/10.1016/j.tube.04), 2014, 001
- [4] Sarathy Jp, Gruber G, Dick T. Re-Understanding The Mechanisms Of Action Of The Anti-Mycobacterial Drug Bedaquiline. *Antibiotics*, 8(4), 2014.
- [5] Who. Warning: This Report Is Out-Of-Date. In Particular, The Entire Time-Series Of Tb Disease Burden Estimates Are Updated Every Year. For The Latest Data And Analysis, Please See The Most Recent Edition Of The Global Tb Report. *Glob Tuberc Control.* 2016;
- [6] Diacon Ah, Pym A, Grobusch Mp, De Los Rios Jm, Gotuzzo E, Vasilyeva I, Et Al. Multidrug-Resistant Tuberculosis And Culture Conversion With Bedaquiline. *N Engl J Med.* 371(8), 2014, 723–32.
- [7] Cohen K, Maartens G. A Safety Evaluation Of Bedaquiline For The Treatment Of Multi-Drug Resistant Tuberculosis. *Expert Opin Drug Saf*

- [Internet]. 2019; 18(10): 875–82. Available From: <https://doi.org/10.1080/14740338.2019.1648429>
- [8] Brown-Elliott Ba, Philley J V., Griffith De, Thakkar F, Wallace Rj. In Vitro Susceptibility Testing Of Bedaquiline Against Mycobacterium Avium Complex. *Antimicrob Agents Chemother.* 61(2), 2014, 1–11.
- [9] Oh Ct, Moon C, Park Ok, Kwon Sh, Jang J. Novel Drug Combination For Mycobacterium Abscessus Disease Therapy Identified In A Drosophila Infection Model. *J Antimicrob Chemother.* 69(6), 2014, 1599–607.
- [10] Fox Gj, Menzies D. A Review Of The Evidence For Using Bedaquiline (Tmc207) To Treat Multi-Drug Resistant Tuberculosis. *Infect Dis Ther.* 2(2), 2013, 123–44.
- [11] Liu K, Li F, Lu J, Liu S, Dorko K, Xie W, *et al.* Bedaquiline Metabolism: Enzymes And Novel Metabolites. *Drug Metab Dispos.* 42(5), 2014, 863–6.
- [12] Diacon Ah, Donald Pr, Pym A, Grobusch M, Patientia Rf, Mahanyele R, *Et Al.* Randomized Pilot Trial Of Eight Weeks Of Bedaquiline (Tmc207) Treatment For Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, And Effect On The Emergence Of Drug Resistance. *Antimicrob Agents Chemother.* 56(6), 2012, 3271–6.
- [13] Svensson Em, Acharya C, Clauson B, Dooley Ke, Karlsson Mo. Pharmacokinetic Interactions For Drugs With A Long Half-Life—Evidence For The Need Of Model-Based Analysis. *Aaps J.* 18(1), 2016, 171–9.
- [14] Us Food And Drug Administration Center For Drug Evaluation And Research. 204384orig1s000medr_.Pdf. *Clin Pharmacol Biopharm Rev.*
- [15] Chahine Eb, Karaoui Lr, Mansour H. Bedaquiline: A Novel Diarylquinoline For Multidrug-Resistant Tuberculosis. *Ann Pharmacother.* 2014; 48(1): 107–15.
- [16] Rouan Mc, Lounis N, Gevers T, Dillen L, Gilissen R, Raoof A, *Et Al.* Pharmacokinetics And Pharmacodynamics Of Tmc207 And Its N-Desmethyl Metabolite In A Murine Model Of Tuberculosis. *Antimicrob Agents Chemother.* 56(3), 2016, 1444–51.
- [17] Costa A, Pinheiro M, Magalhães J, Ribeiro R, Seabra V, Reis S, *et al.* The Formulation Of Nanomedicines For Treating Tuberculosis. *Adv Drug Deliv Rev* [Internet]. 2016; 102: 102–15. Available From: <http://dx.doi.org/10.1016/j.addr.2014.012>
- [18] Hards K, Robson Jr, Berney M, Shaw L, Bald D, Koul A, *et al.* Bactericidal Mode Of Action Of Bedaquiline. *J Antimicrob Chemother.* 70(7), 2015, 2028–37.

- [19] 19. Ismail Na, Omar S V., Joseph L, Govender N, Blows L, Ismail F, *et al.* Defining Bedaquiline Susceptibility, Resistance, Cross-Resistance And Associated Genetic Determinants: A Retrospective Cohort Study. *Ebiomedicine* [Internet]. 2018; 28: 136–42. Available From: <https://doi.org/10.1016/j.ebiom.01.2018.005>
- [20] Diacon Ah, Dawson R, Von Groote-Bidlingmaier F, Symons G, Venter A, Donald Pr, *et al.* Randomized Dose-Ranging Study Of The 14-Day Early Bactericidal Activity Of Bedaquiline (Tmc207) In Patients With Sputum Microscopy Smear-Positive Pulmonary Tuberculosis. *Antimicrob Agents Chemother.* 57(5), 2013, 2199–203.
- [21] Esposito S, Bianchini S, Blasi F. Bedaquiline And Delamanid In Tuberculosis. *Expert Opin Pharmacother.* 16(15), 2015, 2319–30.
- [22] Svensson Em, Murray S, Karlsson Mo, Dooley Ke. Rifampicin And Rifapentine Significantly Reduce Concentrations Of Bedaquiline, A New Anti-Tb Drug. *J Antimicrob Chemother.* 70(4), 2014, 1106–14.