TO:
Dries de Lange, BestMed
Bobby Ramasia, Bonitas
Charlene Schoeman, Cape Medical Plan
T Mfaba, Commed
Johan Pretorius, Compcare Wellness
Jonathan Broomberg, Discovery Health
Jeremy Yatt, Fedhealth Medical Scheme
Gunvant Goolab, GEMS
Shrivaar Singh, Genesis Medical Scheme
Dawid van Zyl, Hosmed Medical Scheme
JH Greyling, Keyhealth Medical Scheme
Andrew Edwards, Liberty Medical
RJ Hallowell, Makoti Medical Scheme
Anton Rijnen, Medihelp
Mike Neubert, Medimed Medical Scheme
Angela Blackburn, Medshield
Nicolaas Kruger, Momentum Health and Topmed Medical Scheme
Graham Anderson, Profmed
Mark Arnold, Resolution Health
Christo Becker, Selfmed Medical Scheme
Grant Newton, Sizwe Medical Fund
Theunis Bothma, Spectramed
Jeff Slome, Suremed Health
Rowan Laird, Thebemed

11 December 2014

RE: Coverage of linezolid for drug-resistant tuberculosis by Medical Schemes

We write to you in regard to the responsibility upon medical schemes to cover the costs of the drug linezolid (also known by the brand name "Zyvoxid,") for the treatment of drug-resistant tuberculosis ("DR-TB").

It has come to our attention that some medical schemes may be refusing, in certain cases, to cover the cost of this medication despite a legal and ethical responsibility to do so as well as the potentially devastating public health consequences of refusing coverage.[1]

In the below, we provide an overview of tuberculosis (TB), which is the leading cause of death in South Africa[2] and DR-TB, of which there is a growing epidemic in South Africa. We also explain the importance of linezolid as an option for the treatment of DR-TB. We present the legal duty of health schemes to cover treatment with linezolid and explain a recent decision by Discovery Health to cover linezolid treatment for a patient.

This information clearly demonstrates that, when linezolid is prescribed in adherence with the National Department of Health's "Management of Drug-Resistant Tuberculosis Policy Guidelines, 2012" guidelines, there is no medical, ethical or legal basis for a refusal by a medical scheme to provide coverage to its members.

We have consulted with the National Department of Health and they agree with our assessment.

As such, we detail here our request for your medical scheme to:

1) Provide in writing its policy on providing coverage for linezolid (at the full dose and length prescribed by the treating clinician or specialist);
2) Commit in writing to providing coverage for treatment with linezolid for your members as required by law and policy; and
3) Refund any amounts paid for linezolid by your members on an out-of-pocket basis because your medical scheme previously denied them coverage.

[1] An article published on Health-e News on 3 October 2014 reported that Discovery, the Government Employees Medical Scheme, Fedhealth and Momentum had indicated to Health-e News that "that while they had previously paid for some patients to receive the drug, the decision to do so was taken on a case-by-case basis largely because linezolid was not considered as standard therapy as per national guidelines." Available at http://www.health-e.org.za/2014/10/03/xdr-tb-patients-smuggle-pills-treatment-priced-reach/

[2] Available on page 38 of the following: http://www.statssa.gov.za/publications/p03093/p030932010.pdf

Overview of Drug-Resistant TB

TB is the leading cause of death in South Africa, and the country has a growing epidemic of DR-TB. Every year, approximately 15,000 people are diagnosed with multidrug-resistant TB (MDR-TB), with over 1,000 of these people found to have extensively drug-resistant TB (XDR-TB).[3]

MDR-TB is resistant to isoniazid and rifampicin—the two most important TB drugs—while XDR-TB is also resistant to two of the most effective second-line medicines used to treat MDR-TB (a fluoroquinolone and a second-line injectable agent). Rapid and prolonged treatment with multiple drugs to which the strain of TB is susceptible is essential to protect patient health, to prevent the development of further resistance, and to prevent transmission.

Of those patients who start on treatment, only about half of those patients with MDR-TB and less than 20% of patients with XDR-TB are cured. DR-TB treatment consists of up to 30 pills a day for at least two years, with painful injections for the first six months of treatment, and many patients suffer terrible side effects including permanent deafness. DR-TB treatment must consist of multiple drugs as part of a regimen, but options of drugs to include in designing adequately strong regimens for patients with extensive drug resistance are extremely limited. Doctors' ability to use the most effective drugs available to design adequate treatment regimens for complicated DR-TB cases will be crucial in supporting patients to adhere to treatment, and limiting the spread of the epidemic in South Africa.

Overview of the Efficacy and Clinical Use of Linezolid

Linezolid is a treatment option that can be used effectively within a multi-drug regimen for DR-TB patients in whom standard second-line TB treatment is unlikely to provide an adequate chance of a cure. While not originally developed to treat TB, a number of clinical studies have found the antibiotic to be effective against DR-TB.[4] In Khayelitsha, Western Cape, the organisation Doctors Without Borders (MSF) has found linezolid-containing regimens to be effective in treating DR-TB in both HIV-positive and HIV-negative individuals.[5]

In its 2011 guidelines, the World Health Organisation recommends linezolid as a Group 5 drug for selected DR-TB cases.[6] The drug is similarly recognised in the South African National Department of Health's "Management of Drug-Resistant Tuberculosis Policy Guidelines, 2012" ("the Guidelines").[7]

Current Use of Linezolid in South Africa's Public and Private Sectors

At present, the pharmaceutical company Pfizer is the only registered manufacturer of linezolid in South Africa, and markets the drug under the brand name Zyvoxid. A select few healthcare providers in South Africa offer linezolid to DR-TB patients in line with national guidelines and protocols. A patient will take one 600mg pill of linezolid daily for up to two years, though a clinician may choose to reduce the daily dose or duration of treatment on a patient-specific basis.

---

[3] https://www.msf.org.za/sites/msf.org.za/files/Publications/Strategic_overview_of_MDR_TB_RSA.pdf

[4] The following systematic reviews outline the success of linezolid when used in DR-TB regimens: https://www.msf.org.za/sites/msf.org.za/files/Publication/Documents/Linezolid_complicated_drtb.pdf and https://www.msf.org.za/sites/msf.org.za/files/Publication/Documents/Efficacy_safety_and_tolerability.pdf

[5] https://www.msf.org.za/msf-publications/msf-reports-promising-results-treating-xdr-tb-patients-with-linezolid-primary-care

[6] http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf?ua=1

[7] Available at: http://www.hst.org.za/publications/management-drug-resistant-tuberculosis-policy-guidelines

In the private sector market, the brand-name version of linezolid costs approximately R757 per pill.[8] Previously, the National Department of Health has purchased brand-name linezolid for the public sector through the antibiotics tender for R288 per pill—but this tender has expired. The Department of Health has requested bids to supply linezolid through the TB drugs tender, but the only eligible supplier, Pfizer, has chosen not to bid.

Generic versions of linezolid are manufactured in India at significantly lower prices than Pfizer's product. In 2013, the UK regulatory authority granted quality approval for a generic product from manufacturer, Hetero, which is available through the Global Drug Facility (GDF) pooled procurement mechanism for US$6.90 per pill.[9] This product is also currently under fast-track review by the South African Medicines Control Council (MCC) since June 2013. Four other generic linezolid manufacturers have tentative approval from the US Food and Drug Administration, and may also have filed registration dossiers for generic versions of linezolid in South Africa. There is potential for linezolid prices offered to the GDF and countries to drop to even lower levels if demand increases and healthy competition among multiple suppliers exists.

MSF applied for permission under Section 21 of the "Medicines and Related Substances Control Act 101 of 1965" to use Hetero's linezolid product in its Khayelitsha operations, while the product was pending registration at the MCC. This permission was granted by the MCC on June 26, 2014, and set a precedent for other healthcare providers in South Africa to file for similar permission to access a more affordable linezolid product. MSF purchases linezolid directly from Hetero at a price of US$8 (~R88) per pill.

THE LEGAL DUTY TO COVER TREATMENT WITH LINEZOLID

Section 27 of the Constitution confers on everyone the right of access to health care services. One of the measures in place to give effect to this right is the Medical Schemes Act 131 of 1998 ("the Act"). The Act, and the General Regulations promulgated in terms of the Act ("the Regulations")[10] provide for prescribed minimum benefits ("PMBs") in respect of which medical schemes have no discretion. All medical schemes are required by the Act and its regulations to cover costs related to the diagnosis, treatment and care of PMBs.

TB is a PMB in terms of the Act. Refusal by a medical scheme to cover DR-TB treatment is therefore a denial of the right of access to healthcare services as entrenched by section 27 of the Constitution and a breach of the Act and Regulations.

Regulation 7 of the Regulations defines a PMB as:

> *[meaning] the benefits contemplated in section 29(1)(o) of the Act, and consist of the provision of the diagnosis, treatment and care costs of;*
>
> *(a) the Diagnosis and Treatment Pairs listed in Annexure A, subject to any limitations listed in Annexure A; and*
> *(b) Any emergency medical condition[.]*

[8] Price from the November 19th version of the Medicines Price Registry Database. Available at: http://mpr.gov.za/PublishedDocuments.aspx#DocCatId=21
[9] http://www.msfaccess.org/sites/default/files/MSF_TB_Report_UTM3rdEdition-2013.pdf
[10] Regulations in terms of the Medical Schemes Act 131 of 1998 GN 1262 GG 20556 of 20 October of 1999

Annexure A to the Regulations provides that TB is a PMB and that the treatment for TB is "Diagnosis and acute medical management, successful transfer to maintenance therapy *in accordance with DoH guidelines*." [emphasis added]. Neither the Regulations nor Annexure A distinguish between drug-susceptible and drug-resistant strains of TB.

In terms of Regulation 8(1), medical schemes "must pay in full, without co-payment or the use of deductibles, the diagnosis, treatment and care costs of the prescribed minimum benefit conditions." Regulation 10(6) moreover provides that funds in a member's medical savings account may not be used to cover the costs of a PMB.

In sum, the Regulations require the treatment of TB to be covered as a PMB in accordance with guidelines issued by the DoH. The controlling guidelines in regard to drug-resistant TB are the 2012 Guidelines mentioned above. National Department of Health's "Management of Drug-Resistant Tuberculosis Policy Guidelines, 2012" ("the Guidelines").

Considering the need for each person with XDR-TB to be treated with a regimen of medication with the potential to be effective against his or her particular strain of TB, the Guidelines emphasize that clinicians must tailor treatment regimens to each particular case. Section 8.1 of the Guidelines provides that:

> *By definition, two key classes of second-line anti-TB drugs are compromised in XDR-TB. Individualised treatment regimens are therefore essential and must be designed according to DST* [drug susceptibility testing] *results and history of previous drug use*. [definition of DST added].

Section 8.2 of the Guidelines further explains that the "rationale for individualised treatment regimens in the treatment of patients with XDR-TB is that they have to receive drugs that the strain is susceptible to and exclude those that they are resistant to."

Section 8.2 of the Guidelines also provides a set of "principles" that "must be applied when designing XDR-TB regimens." One principle is that "at least four drugs expected or known to be effective or [that the] patient has not been exposed to should be included."

In sum, the essential challenge in treating XDR-TB is developing a treatment regimen consisting of drugs that are expected or known to be effective in a particular case. Therefore, the Guidelines provide instruction as to how to develop effective treatment regimens. Section 8.2 of the Guidelines instructs doctors to "use Group 5 drugs as needed." It establishes as a "principle" that "Group 5 drugs should be considered [in] cases where adequate regimens are impossible to construct with available drugs from the other groups and you need to strengthen the regimen."

Section 7.6 of the Guidelines identifies linezolid as a Group 5 drug and section 7.5 explains that "Linezolid is an oxazolidinone antibacterial. It showed good activity against *M. tuberculosis* in vitro and has been used with success in MDR/XDR-TB patients in several case reports. Linezolid should be considered if cost permits."

The issue of costs

The stipulation in the Guidelines that "Linezolid should be considered if cost permits", must be interpreted through the lens of the constitutional rights of access to healthcare

services and equality, the current state of science and available treatment discussed above as well as the Act and its regulations.

As established above, regulation 8(1) of the Regulations makes clear that medical schemes must "must pay in full, without co-payment or the use of deductibles, the diagnosis, treatment and care costs of the prescribed minimum benefit conditions."

A medical scheme cannot abdicate this duty simply because it is economically convenient to do so. Medical Schemes have the right in terms of regulation 8(4) to employ "appropriate interventions aimed at improving the efficiency and effectiveness of health care provision." However, outright refusal of coverage for the treatment of a PMB would clearly fall outside of the scope of "appropriate interventions" as it would negate the fundamental import of PMBs, particularly where no alternative treatment is available.

In addition, Explanatory Note to Annexure A of the Regulations provides that

> *A review shall be conducted at least every two years by the Department that will involve the Council for Medical Schemes, stakeholders, Provincial health departments and consumer representatives. In addition, the review will focus specifically on development of protocols for the medical management of HIV/AIDS. These reviews shall provide recommendations for the revision of the Regulations and Annexure A on the basis of—*
>
> *(i) inconsistencies or flaws in the current regulations;*
> *(ii) the cost-effectiveness of health technologies or interventions;*
> *(iii) consistency with developments in health policy; and*
> *(iv) the impact on medical scheme viability and its affordability to Members.*

Thereby, the Department has been provided a mechanism through which medical schemes are able to submit any concerns with the duties created by the Regulations. If, for example, a medical scheme were to be of the belief that an obligation created by the Regulations threatens its viability or affordability, or that a treatment it must fund in terms of the Regulations is not a cost-effective intervention, the reviews established by the Explanatory Note to Annexure A are designed specifically for the purpose of bringing those concerns to the attention of the Department of Health.

ANDALEEB RINQUEST AND DISCOVERY HEALTH MEDICAL SCHEME

We welcome and wish to bring to your attention to recent decision by Discovery Health Medical Scheme to provide coverage for linezolid for Mrs Andaleeb Rinquest-January. Discovery Health initially refused to cover Mrs Rinquest-January's treatment but subsequently agreed to provide coverage after Mrs Rinquest-January disputed the decision.

We are concerned that Discovery initially denied Mrs Rinquest-January coverage, especially as her doctor, Prof Paul Willcox, a recognised leading expert in the field, had explained to Discovery that linezolid was the "only drug which [would] potentially cure" her. We are also concerned, as indicated above, that Discovery and other medical schemes are reported to have admitted that they refuse to cover linezolid in some cases despite their legal obligations.

When linezolid is prescribed in adherence with the Guidelines, there is no medical, ethical or legal basis for a refusal to provide coverage.

CONCLUSION
As such, we again request your medical scheme to:

1) Provide in writing its policy on providing coverage for linezolid (at the full dose and length prescribed by the treating clinician or specialist);
2) Commit in writing to providing coverage for treatment with linezolid for your members as required by law and policy; and
3) Refund any amounts paid for linezolid by your members on an out-of-pocket basis because your medical scheme previously denied them coverage.

Please direct all correspondence in this matter to Ms. Erica Lessem via erica.lessem@treatmentactiongroup.org

Sincerely,

Organizational Signatories
AIDS and Rights Alliance for Southern Africa (ARASA)
Community Research Advisors Group
Global Coalition of TB Activists
Global TB Community Advisory Board
Médecins Sans Frontières Access Campaign
Médecins Sans Frontières Khayelitsha Project
Médecins Sans Frontières South Africa Mission
RESULTS Australia
RESULTS Educational Fund
RESULTS UK
Section 27
STOPAIDS, UK
Treatment Action Campaign
Treatment Action Group
TB Proof
University of Zambia - University College London Medical School Research & Training Programme

Individual Signatories*
Sr. Pat Bond, Occupational MDR-TB survivor and Renal Dialysis Sister (retired), South Africa
Dr. Greg Calligaro, Division of Pulmonology, Department of Medicine, University of Cape Town**,** Lung Infection and Immunity Unit, University of Cape Town Lung Institute, South Africa
Dr. Vivian Cox, Deputy Field Coordinator, Médecins Sans Frontières Khayelitsha, South Africa
Prof. Keertan Dheda, Head, Lung Infection and Immunity Unit and Division of Pulmonology, University of Cape Town, South Africa
Dr. Angela Dramowski, Occupational TB survivor and Infectious Diseases Paediatrician, Stellenbosch University, South Africa
Koot Kotze, TB activist and medical student, Stellenbosch University, South Africa

Cynthia Lee, TB advocate and member of the Community Research Advisors Group, USA
Dr. Gwinyai Masukume, TB Proof member, University of the Witwatersrand Johannesburg, South Africa
Dr. Thato Mosidi, Occupational XDR-TB survivor and Research Medical Officer, South Africa
Heena Narotam, TB activist and medical student, Stellenbosch University, South Africa
Dr. Nesri Padayatchi, Deputy Director CAPRISA; Clinician, Scientist and MDR TB specialist, Durban, South Africa
Dr. Jurgens Peters, MBChB, MPH, MSc, DTM&H, FRSPH, UK
Dr. Alexander Pym, Associate Investigator, K-RITH: KwaZulu-Natal Research Institute for Tuberculosis & HIV, South Africa
Andaleeb Rinquest, XDR-TB Patient, Cape Town, South Africa
Prof. Simon Schaaf, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University Cape Town, South Africa
Dr. Barbara Seaworth, University of Texas Health Northeast, USA
Morgan Scholtz, XDR-TB patient, Western Cape, South Africa
Helene-Mari van der Westhuizen, TB activist and medical student, Stellenbosch University, South Africa
Dr. Arne von Delft, living with latent TB, Public Health Medicine Registrar, University of Cape Town, South Africa
Dr. Dalene von Delft, Occupational MDR-TB survivor and Emergency Medicine Medical Officer, South Africa
Dr. Rachel Weiss, Director Clinical Skills Centre, University of Cape Town, South Africa
Prof. Paul Willcox, Pulmonologist and drug-resistant TB specialist, University of Cape Town Private Academic Hospital, Cape Town, South Africa
Dr. Bart Willems, Occupational TB survivor and Public Health Medicine Registrar, Stellenbosch University, South Africa

**For individual signatories, institutions are listed as affiliations only, and do not reflect institutional endorsement*

ARASA AIDS & Rights Alliance for Southern Africa

CRAG TB Community Research Advisors Group

Global Coalition of TB Activists

TBCAB GLOBAL TB COMMUNITY ADVISORY BOARD

ACCESS CAMPAIGN MEDECINS SANS FRONTIERES

MEDECINS SANS FRONTIERES DOCTORS WITHOUT BORDERS

Head of Mission, Andrew Mews, for Doctors Without Borders (MSF) South Africa Mission

RESULTS the power to end poverty

www.results.org.au

RESULTS the power to end poverty

+SECTION27 catalysts for social justice

TAC TREATMENT ACTION CAMPAIGN

TAG Treatment Action Group

TB PROOF?

www.facebook.com/TBproof | www.tbproof.org

UNZA-UCLMS UCL Research & Training Programme