CANCER ALLIANCE

Collective Voices for Cancer in South Africa

MOTIVATION FOR PROMPT REGISTRATION

OF

TRASTUZUMAB BIOSIMILARS IN SOUTH AFRICA

SUBMITTED BY

THE CANCER ALLIANCE OF SOUTH AFRICA

TO

THE SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

JULY 15, 2019

I. EXECUTIVE SUMMARY

1. The Cancer Alliance of South Africa submits this memorandum in support of its request that SAHPRA promptly register biosimilars of the breast cancer medicine trastuzumab for which manufacturers have submitted New Medicine Launch Forms. We commend SAHPRA for recently approving Mylan's biosimilar and stress the importance of swiftly approving the four remaining applications submitted by other trastuzumab biosimilar manufacturers.

2. The need for registration is now the critical barrier to trastuzumab biosimilars in South Africa, as the main patents that protected Herceptin, the originator's trastuzumab product, have expired. Without approval, biosimilar manufacturers will not commence the six- to seven-month process of setting up distribution of their products, resulting in further delay for patients who need but cannot afford this life-saving treatment.

3. With only one trastuzumab biosimilar, the reduction in price is likely to be modest. It is critical that SAHPRA register promptly all biosimilars that satisfy the regulatory requirements, as the price of medicines depends strongly on the number of competing suppliers.

4. Biosimilar competition will have major health and economic benefits:

- Trastuzumab is the standard of care for HER2-positive breast cancer internationally and is on the Essential Medicines Lists of the World Health Organization and the South African Department of Health. However, because South African prices are so high, utilisation in both the private and public healthcare sectors is highly restricted:
    - In the private sector, only about one fifth of patients who should be treated with trastuzumab currently receive treatment, yet trastuzumab is one of the largest cost drivers for medical aid schemes;
    - In the public sector, trastuzumab was only recently added to the list of essential medicines. To date, utilisation is low and cost continues to be an obstacle;

- For private medical schemes and the patients they cover, biosimilar competition could reduce the cost of trastuzumab by more than 80%. Such a reduction would greatly benefit existing patients and allow all private sector patients who need trastuzumab to be treated with no increase in total expenditure over current levels;
- Although the South African public sector's tender price for trastuzumab is below that paid by the private sector, biosimilars could bring about a further price reduction of about 45%, which would allow almost twice as many patients to be treated without increasing expenditure on trastuzumab. Biosimilars would also ensure a reliable and affordable supply that does not depend exclusively on the originator;
- Competition among biosmilars is essential to driving the price low enough for increased expenditure on trastuzumab to be cost-justified, given the limited budgets of both medical schemes and the public sector;
- The need for trastuzumab is increasing, as the incidence of breast cancer is rising and trastuzmab is being introduced at public sector treatment centers. The benefits of SAHPRA approving multiple trastuzumab biosimilars will thus increase greatly over time.

II. THE CANCER ALLIANCE

5. The Cancer Alliance is a collective group of 29 cancer control non-profit organisations and cancer advocates brought together under a common mandate, to provide a platform of collaboration for cancer civil society to speak with one voice and be a powerful tool to affect change for all South African adults and children affected by cancer. Member organisations of the Cancer Alliance work closely with people affected by cancer, often in underserved communities, providing a range of support services. Many of the individuals working or volunteering with member organisations of the Cancer Alliance are cancer survivors themselves. Under the umbrella of the Cancer Alliance, member groups jointly undertake advocacy on issues related to cancer prevention, detection and treatment.

6. Since 2016, the Cancer Alliance as part of Fix the Patent Laws, a coalition seeking reform of the country's patent laws to improve medicine access, has led advocacy efforts by to bring about affordable and equitable access to trastuzumab in South

Africa under the Tobeka Daki Trastuzumab Access Campaign. Since the campaign was launched, South Africa's Department of Health has taken important steps to ensure trastuzumab access for women with HER2-positive early breast cancer. However, as discussed below, the medicine's high cost continues to be a major barrier.

III. HER2-POSITIVE BREAST CANCER, TRASTUZUMAB, AND COST AS A BARRIER TO ACCESS

A. HER2-Positive Breast Cancer

7. Breast cancer is the second most common cancer globally, and the most common cancer faced by women.[1] Breast cancer is the leading cause of cancer death faced by women in developing countries and the 5th leading cause of cancer death globally.[2] In South African women, breast cancer is the second leading cause of cancer death after cervical cancer.[3] Approximately 1 in 29 women in South Africa will experience breast cancer in their lifetime.[4] While Africa generally experiences lower rates of breast cancer than other regions, incidence rates are increasing in the region[5] and in South Africa.[6]

8. Approximately 1 in 5 women diagnosed with breast cancer are HER2-positive – meaning that the human epidermal growth factor receptor (HER2) is overexpressed in the breast cancer tumour.[7] HER2 overexpression is associated with more aggressive disease, higher rates of recurrence and higher mortality rates than HER2-negative tumours.[8] "[P]atients with breast cancer and tumors over-expressing HER2 have a particularly dire prognosis when treated with chemotherapy alone, since these

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[1] Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D. and Bray, F., "Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012," *Int. J. Cancer* (2015), 136: E359–E386. doi:10.1002/ijc.29210 (Ferlay, *et al.*).
[2] Ferlay, *et al.*
[3] http://www.who.int/cancer/country-profiles/zaf_en.pdf?ua=1.
[4] http://www.cansa.org.za/womens-health/.
[5] http://www.who.int/cancer/country-profiles/zaf_en.pdf?ua=1.
[6] http://www.gov.za/international-breast-cancer-month-2015.
[7] Mitri Z, Constantine T, O'Regan R., "The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy," *Chemotherapy Research and Practice* (2012) doi:10.1155/2012/743193 (Mitri, *et al.*).
[8] Mitri, *et al.*

cancers are aggressive and have a high rate of metastatic spread."[9] International evidence has demonstrated that HER2 overexpression is generally more common among younger women with breast cancer than older women.[10, 11] Evidence from South Africa indicates that young black women may be more at risk for developing breast cancer at a younger age and HER2-enriched breast cancer than other racial groups.[12]

B. Trastuzumab Formulations, Approved Indications, and Treatment Regimens

9. As SAHPRA knows, trastuzumab is an injectable humanized monoclonal antibody which binds to the human epidermal growth factor receptors that are overexpressed in women with HER2-positive cancer and thus inhibits proliferation of tumour cells.[13] The standard, accepted treatment regimen consists of intravenous (IV) injections using 440 mg vials of trastuzumab at 1- and 3-week intervals over the course of one year for adjuvant treatment of early and metastatic HER2-positive breast cancer.[14] In addition, a formulation of trastuzumab for subcutaneous delivery has been introduced and other package sizes and dosing regimens exist.[15] However, the current biosimilar

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[9] Union for International Cancer Control and Dana-Farber Cancer Institute Center for Global Cancer Medicine, *Review of the available evidence on Trastuzumab for Inclusion in the WHO Essential Medicines List as an anti-neoplastic agent*, January 9, 2013 ("UICC-DF Review of Evidence for Inclusion in WHO EML" available at https://www.who.int/selection_medicines/committees/expert/19/applications/Trastuzumab1_8_2_A_Ad_Final.pdf?ua=1), p. 4

[10] Cronin K, Harlan L, Dodd K, Abrams J, and Ballard-Barbash R., "Population-based Estimate of the Prevalence of HER-2 Positive Breast Cancer Tumors for Early Stage Patients in the US," *Cancer Investigation*, Vol. 28, Iss. 9,2010.

[11] Anders CK, Johnson R, Litton J, Phillips M, Bleyer A., "Breast Cancer Before Age 40 Years," *Seminars in oncology* (2009), 36(3):237-249. doi:10.1053/j.seminoncol.2009.03.001.

[12] See discussion in the Cancer Alliance motivation for provision of trastuzumab in South Africa's public sector to women with HER2-positive breast cancer, 2016, pp. 2-3 and the sources cited there: Cubash H., *et al.*, "Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa," *Breast Cancer Res Treat.* 2013 Jul., 140(1): 177–186; Dickens C, *et al.*, "Racial Comparison of Receptor-Defined Breast Cancer in Southern African Women: Subtype Prevalence and Age–Incidence Analysis of Nationwide Cancer Registry Data," *Cancer Epidemiol Biomarkers Prev*, November 1 2014 (23) (11) 2311-2321; DOI: 10.1158/1055-9965.EPI-14-0603; Montemurro, *et al.*, "Potential biomarkers of long-term benefit from single-agent trastuzumab or lapatinib in HER2-positive metastatic breast cancer," *Molecular Oncology*, Volume 8, Issue 1, February 2014, Pages 20–26; and Matatiele PR & Van den Heever WMJ, "Breast cancer profiles of women presenting with newly diagnosed breast cancer at Universitas Hospital (Bloemfontein, South Africa)," *SA Fam Pract.* 2008, Volume 50 No 6.

[13] http://www.herceptin.com/breast/metastatic.

[14] See, for example: UICC-DF Review of Evidence for Inclusion in WHO EML, p. 6;. Healio: *HemOnc Today*, "One year of adjuvant trastuzumab remains standard of care for HER2-positive breast cancer," June 14, 2019 (https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bd7ee87a9-b9b6-4842-a968-099a87164849%7D/one-year-of-adjuvant-trastuzumab-remains-standard-of-care-for-her2-positive-breast-cancer).

[15] For IV injection, a 150 mg vial for single use is available in addition to the standard 440 mg vial, which may be used to deliver more than one dose. The formulation of trastuzumab for subcutaneous injection is available in 600

applicants have, to our knowledge, sought to register only the IV formulation in South Africa and the standard IV regimen is generally the only one considered in health economic analyses.[16] For these reasons, the cost-effectiveness analysis in this memo considers only the standard IV regimen.

C. Internationally, Trastuzumab Is the Standard of Care and an Essential Medicine

10. A recent World Health Organization (WHO) report, after noting that for all too many cancer medicines the prolongation and/or improvement in the quality of life is very modest or based on limited evidence, highlights trastuzumab as having transformed treatment of HER2-positive breast cancer, with well documented efficacy leading to substantial improvement in health outcomes.[17] Expert bodies internationally identify treatment with trastuzumab as being supported by robust evidence of important improvement in health outcomes over the available alternatives of chemotherapy alone:[18] For example, the Union for International Cancer Control and Dana-Farber Cancer Institute Center for Global Cancer Medicine concluded from a review of the available evidence on trastuzumab in 2013 that "The magnitude of the treatment effect proved to be similar and consistent across different clinical trials: 50% decrease in rates of recurrence and 30% reduction in breast cancer related mortality. As far as

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mg vials, dosed every three weeks for one year or until disease recurrence or unmanageable toxicity, whichever occurs first. For metastatic breast cancer and metastatic gastric cancer, the length of treatment may not be predetermined, but should continue as long it controls progression of the disease (see, for example, Proposal for the Inclusion of Trastuzumab in the WHO Model List of Essential Medicines for the Treatment of HER2-Positive Breast Cancer, 14 January 2013 (KEI-UCSD Proposal for Inclusion in WHO EML, available at https://www.who.int/selection_medicines/committees/expert/19/applications/Trastuzumab2_8_2_A_Ad_Final.pdf), p. 8).

[16] See, for example: World Health Organization, *Technical Report: Pricing of cancer medicines and its impacts*, 2018 (WHO, *Pricing of Cancer Medicines*), p. 78; Noga Gershon, Yakir Berchenko, Peter S. Hall and Daniel A. Goldstein, "Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer," *Cost Effectiveness and Resource Allocation*, (2019) 17:5 (Gershon, *et al.*); R P Abratt, "Cost considerations in determining the affordability of adjuvant trastuzumab in breast cancer," *SAMJ* October 2016, Vol. 106, No. 10, 981 – 982 (Abratt, Cost Considerations).

[17] World Health Organization, *Technical Report: Pricing of cancer medicines and its impacts*, 2018 (WHO, *Pricing of Cancer Medicines*), p. 11.

[18] UICC-DF Review of Evidence for Inclusion in WHO EML, pp. 6 – 8; KEI-UCSD Proposal for Inclusion in WHO EML, pp. 8 – 11; and WHO, *Pricing of Cancer Medicines*, p. 11.

cancer treatments are concerned, this benefit is universally accepted as extremely significant and practice changing."[19]

11. Due to its strong clinical evidence, trastuzumab was established by 2013 as the standard of care for treatment of HER2-positive breast cancer, as reflected in clinical guidelines adopted internationally.[20] More recently, trastuzumab has been added to essential medicine lists around the world. The international benchmark for essential medicine lists is the series of Model Lists of Essential Medicines that the World Health Organisation has been publishing since 1977 "to help countries prioritize and select the medicines to include in their national essential medicines lists and, increasingly, national reimbursable medicines lists."[21] In 2015, in response to "the increasing burden of cancer globally and the very high cure rates now being achieved for some cancers"[22] and expert submissions,[23] the WHO added trastuzumab to its Essential Medicines List for the treatment of early and metastatic HER2-positive breast cancer, along with 20 other cytotoxic medicines for various cancers.[24] As of October 2016, trastuzumab was on the essential medicine lists of 26 countries.[25] Trastuzumab has been included on South Africa's Essential Medicines List for the adjuvant treatment of early stage breast cancer since June 2017.[26]

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[19] UICC-DF Review of Evidence for Inclusion in WHO EML, p. 7.
[20] See, for example, UICC-DF Review of Evidence for Inclusion in WHO EML, pp. 10 – 12.
[21] Jane Robertson, *et al.*, "Essential medicines for cancer: WHO recommendations and national priorities," *Bulletin of the World Health Organization*, 2016;94:735-742. doi: http://dx.doi.org/10.2471/BLT.15.163998 (Robertson, *et al.*).
[22] Robertson, *et al.*
[23] See, for example, regarding trastuzumab, the UICC-DF Review of Evidence for Inclusion in WHO EML and KEI-UCSD Proposal for Inclusion in WHO EML.
[24] Robertson, *et al.*; WHO Model List of Essential Medicines, 19th edition (April 2015) (WHO Model List of Essential Medicines, 2015), p. 23. Trastuzumab and the other cytotoxic medicines were added to the WHO's complementary list, which "presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings" (WHO Model List of Essential Medicines, 2015, Explanatory notes; the complementary list of cytotoxic medicines begins on p. 19 of the Model List).
[25] Robertson, *et al.*. Table 1(https://www.who.int/bulletin/volumes/94/10/BLT-15-163998-table-T1.html).
[26] Republic of South Africa Department of Health (DoH) National Essential Medicines List Committee (NEMLC), *Tertiary and Quaternary Level Essential Medicines List*. June 2019, p. 12. The DoH states that all approved items on the Tertiary List are considered part of the Essential Medicines Lists as long as they are used within the appropriate indication and criteria (Communication with Essential Medicines Programme, DoH).

D. The Price of Herceptin Is a Barrier to Access Internationally and in South Africa

12. In a 2018 report on the pricing of cancer medicines internationally, the WHO specifically called out regimens containing Herceptin (the brand name of the originator's version of trastuzumab) for their high cost internationally and in South Africa particularly, stating that "a course of standard (adjuvant) treatment for early stage HER2-positive breast cancer (Adjuvant AC-TH) would cost about 10 years of average annual wages in India and South Africa, and 1.7 years in the USA."[27] The same report, citing an international comparison of the cost of patented cancer drugs published in 2017,[28] shows that, adjusted for purchasing power parity, the cost of trastuzumab was even higher in South Africa than in the US.[29]

13. The high price of Herceptin is a barrier to access internationally. In 2016, Lammers, *et al.* reported that, in a survey of oncologists in the US, Turkey, Brazil, Mexico, and Russia, 45% reported that they would increase their use of trastuzumab if a lower cost biosimilar version were available.[30] The shares of surveyed oncologists who stated that they would increase their use of trastuzumab if the cost were lower were highest in the countries with health coverage most similar to South Africa: 53% in Brazil, 63% in Mexico, and 81% in Russia.[31]

14. The restriction of access due to the high price of Herceptin severely affects African countries. Despite the fact that trastuzumab is the standard of care for early stage HER2-positive breast cancer, Gershon, *et al.* found in a recent study of 11 African countries including South Africa that, based on thresholds for cost effectiveness used

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[27] WHO, *Pricing of Cancer Medicines*, p. 78. For South Africa, this finding is based on the Single Exit Price at which Roche-Genentech supplies Herceptin to the private sector. The use of this price is appropriate inasmuch as almost all treatment with Herceptin in South Africa to date has been in the private sector, despite being substantially restricted by medical aid schemes – see below for further details.
[28] Daniel A. Goldstein, *et al.*, "A global comparison of the cost of patented cancer drugs in relation to global differences in wealth," *Oncotarget*, 2017, Vol. 8, (No. 42), pp: 71548-71555 (Goldstein, *et al.*). Like the WHO report, this study used the Single Exit Price of Herceptin for the private sector, as reported in the Medicine Price Registry.
[29] WHO, *Pricing of Cancer Medicines*, p. 60.
[30] Lammers, Philip, *et al.*, "Barriers to the Use of Trastuzumab for HER2+ Breast Cancer and the Potential Impact of Biosimilars: A Physician Survey in the United States and Emerging Markets." *Pharmaceuticals*, 7.9 (2014): 943–953 (Lammers, *et al.*) at 949.
[31] Lammers, *et al.* at 949.

internationally to allocate funds for health care, trastuzumab is not cost effective in any of the countries analyzed without significant discounts from its current price.[32]

15. Due to the high cost of trastuzumab, its inclusion on essential medicine lists does not ensure access to treatment – rather, it is only a step toward expanding access. Thus, for example, expert bodies calling for trastuzumab to be added to the WHO Essential Medicines List in 2013 motivated their request by noting that "the addition of critical medicines to the WHO Essential Medicines List that appear unaffordable can … serve as a vital lever in expanding access to these medicines and in making them affordable."[33]

16. In South Africa too, trastuzumab's status as an essential medicine does not ensure access. A report on the National Essential Medicine List Review of trastuzumab states that South Africa's National Health Council recommended in April 2017 that trastuzumab be made available for the adjuvant management of early stage breast cancer, but warns that trastuzumab may well be deemed not cost-effective at the current offered price.[34] Consistent with this warning, when the South African Department of Health (DoH) announced in June 2017 that it recommended use of trastuzumab in treatment regimens for HER2+ breast cancer, it stated that its recommendations were subject to affordability:[35] "Whilst evidence shows that the addition of trastuzumab confers substantial risk reduction in recurrence and death," the DoH stated, "[i]t is recommended subject to negotiations with the pharmaceutical providers for a cost that will not compromise care-provision in other sectors of the healthcare system."[36] Since making this announcement, the DoH has negotiated a public sector tender price for trastuzumab that is well below the private sector price –

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[32] Noga Gershon, Yakir Berchenko, Peter S. Hall and Daniel A. Goldstein, "Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer," *Cost Effectiveness and Resource Allocation*, (2019) 17:5 (Gershon, *et al.*).
[33] KEI-UCSD Proposal for Inclusion in WHO EML, p. 3.
[34] National Essential Medicine List Review of trastuzumab as adjuvant treatment for early stage HER-2 positive breast cancer (National EML Review of trastuzumab), p 11 (Review dated 24 February 2016 and updated after April 2017 – see pp. 1, 12), reporting the conclusion reached by the health economic analysis of trastuzumab in adjuvant breast cancer described in Annexure E to the National EML Review, at pp. 4 and 5.
[35] Department of Health, Republic of South Africa, *Breast Cancer Control Policy*, June 2017 (DoH *Breast Cancer Control Policy*), pp. 36 – 39.
[36] DoH *Breast Cancer Control Policy*, p. 37.

however, as shown below, biosimilar competition is needed to reduce the price further, to a level at which treatment with trastuzumab would clearly satisfy cost-effectiveness criteria commonly used to allocate healthcare budgets in developing countries. As discussed further below, the high price of Herceptin has also led to highly restricted coverage by South Africa's medical aid schemes, with only the more expensive schemes providing adequate coverage, even though breast cancer treatment is listed a Prescribed Minimum Benefit (PMB).[37]

17. The barrier to treatment presented by the price of trastuzumab is of particular concern because there are no available substitutes. In 2013, expert bodies calling for trastuzumab to be added to the WHO Essential Medicines List pointed out that there are no less costly drugs which have the important benefit of having been shown to significantly extend the life of patients with advanced HER2-positive breast cancer when added to standard chemotherapy.[38] Similarly, South Africa's National Essential Medicine List Review of trastuzumab in 2016 – 2017 found that there were no similar agents on the EML for the indication of HER2-positive breast cancer.[39]

IV. ACCESS TO TRASTUZUMAB IS SEVERELY LIMITED IN SOUTH AFRICA

18. The vast majority of patients with HER-positive breast cancer in South Africa "do not have access to and do not receive adjuvant trastuzumab, be they cared for in the public sector or the less well-resourced medical scheme options in the private sector" and the cost of trastuzumab is "the major factor determining affordability" of treatment.[40]

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[37] PMB List of All Conditions, available at https://www.medicalschemes.com/medical_schemes_pmb/conditions_covered.htm; file dated 14 August, 2015. PMBs "were established under The Medical Schemes Act 131 of 1998 (the Act) to ensure that members have access to certain minimum health services, regardless of the benefit option they have chosen. … Any [PMB] benefit option that is offered by a medical scheme must be paid in full, without co-payment or the use of deductibles, the diagnosis, treatment and care costs of the prescribed minimum benefit conditions." However, "[m]edical schemes are allowed to have managed care protocols and formularies to manage their financial risk" (Council of Medical Schemes, *CMScript – complete, 2015 collection*, p. 5).

[38] UICC-DF Review of Evidence for Inclusion in WHO EML, p. 4.

[39] National EML Review of trastuzumab, p 11.

[40] R P Abratt, Response to Letter to the Editor, *South African Medical Journal (SAMJ),* January 2017, Vol. 107, No. 1, p. 9 (Abratt, Response to Letter), regarding R P Abratt, "Cost considerations in determining the affordability of adjuvant trastuzumab in breast cancer," *SAMJ* October 2016, Vol. 106, No. 10, 981 – 982 (Abratt, Cost Considerations).

A. Cost of Treatment and Access in the Private Sector: Trastuzumab Is a Major Cost Driver and Is Inadequately Covered by Medical Schemes

19. Trastuzumab is currently available in the South African private sector in its branded, patent-protected form, Herceptin, which is supplied by Roche-Genentech. Like other medicines in South Africa, Herceptin is available at a single, publicly reported price, the Single Exit Price (SEP), which includes the manufacturer price, a logistics fee, and VAT.[41]

20. As of 1 April 2019, the SEP for a 440 mg vial of the IV formulation of Herceptin[42] was R20,318.[43] The manufacturer price accounts for the great bulk of this total: 84% on its own, and 97% when combined with VAT, the amount of which of course increases proportionally with the manufacturer price and logistics fee.[44]

21. The cost of treating HER2-positive breast cancer with Herceptin is appropriately measured on a per-patient basis as the cost of the standard one-year course of IV injections described above. The basic formula for per-patient cost of a course of treatment in the private sector is thus:

Per-Patient Cost = (SEP per vial) X (vials per course of treatment)

22. To estimate per-patient cost, it is necessary to make empirically sound assumptions about average utilisation of trastuzumab and the required number of vials, for three main reasons: first, the recommended dosing of IV injections of Herceptin depends on the weight of the patient;[45] second, the frequency of dosing and size of the dose per

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[41] See, for example: South African Department of Health Medicine Price Registry: Database of Medicine Prices (DoH Medicine Price Registry); Andy Gray and Fatima Suleman, "Pharmaceutical Pricing in South Africa," ch. 14 in Zaheer-Ud-Din Babar, ed., *Pharmaceutical Prices in the 21st Century*, Springer International Publishing, Switzerland 2015, 251 – 265 (Gray and Suleman, Pharmaceutical Pricing) at 255 – 257. A pharmacy dispensing fee, for which the maximum is fixed nationally for each medicine, is also charged in the private sector (See, for example: *https://mpr.code4sa.org/*; Gray and Suleman, Pharmaceutical Pricing at 255 – 257). However, for the purpose of comparing private and public sector prices, only the SEP is included the cost calculations in this memo.

[42] The analysis of costs in this memorandum is limited to the use of trastuzumab in a one-year course of IV treatment. As discussed above, a one-year course of IV injections is the standard regimen for HER2-positive breast cancer.

[43] Prices and dispensing fees reported at *https://mpr.code4sa.org/.*

[44] Calculated from the breakdown of the SEP for a 440 mg vial Herceptin in the DoH Medicine Price Registry, 21 December 2018: manufacturer price, R15,937.95; logistics fee, R596.91; and VAT, R2,480.23.

[45] See, for example, the Highlights of Prescribing Information for Herceptin approved by the United States Food and Drug Administration (US FDA Prescribing Information for Herceptin, available at (https://www.gene.com/download/pdf/herceptin_prescribing.pdf).

kilogram of patients' weight vary over the course of the treatment;[46] third, the great majority of recommended doses do not completely use a 440 mg vial of the IV formulation,[47] so the amount of Herceptin used up in treating each patient depends on the extent to which the residual amounts are used to treat other patients, or possibly for more than one injection for the same patient. Based on different assumptions about patients' average weight and vial usage, a range of 15.76 to 20 440 mg vials for a one-year course of IV treatment is observed in relevant literature.[48] On the advice of a leading South African oncologist, we assume for the purpose estimating treatment costs that the average number of 440 mg vials per course of treatment is 17.[49]

23. As mentioned, Herceptin represents the largest, but not the only, cost of treating HER2-positive breast cancer, as chemotherapy medicines and medical services are also required. However, the alternatives to treatment with trastuzumab are chemotherapy-only regimens for which the cost is similar to that of the chemotherapy used as treatment with trastuzumab.[50] Therefore we, like Gershon, *et al.*, consider only the incremental costs and benefits of trastuzumab in evaluating the cost-effectiveness of treatment regimens that include trastuzumab.[51] Also, like Gershon, *et al.* and Abratt, we do not incorporate in our analysis the heart failure incidence reported in trastuzumab clinical trials.[52] We understand that cardiac effects of treatment with trastuzumab are reversible and are not associated with increased mortality;[53]

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[46] See, for example, US FDA Prescribing Information for Herceptin.
[47] This can be seen by comparing the 440 mg vial size with the implied numbers of mg of trastuzumab at different stages of the 1-year adjuvant dosing regimen based on the US FDA Prescribing Information for Herceptin and the 60 kg average weight of African women reported by Gershon, *et al.*, p. 4.
[48] 15.76 vials is calculated from the assumptions adopted by Gershon, *et al.*; 20 vials is calculated from the assumptions adopted by Catherine Tomlinson, *et al.*, *Exploring Patent Barriers to Cancer Treatment Access in South Africa: 24 Medicine Case Studies*, prepared for the Cancer Alliance and Fix the Patent Laws!, October 2017, at p. 37.
[49] Communication with Prof. Paul Ruff, professor of oncology at the University of the Witwatersrand Medical School, June 2019.
[50] Gershon, *et al.*, p. 4.
[51] Gershon, *et al.*, p. 4.
[52] Gershon, *et al.*, p. 3; Abratt, Cost Considerations, p. 981.
[53] Gershon, *et al.*, p. 3.

however, a more complete analysis would seek to account for these effects and associated incremental healthcare costs.[54]

24. At the current SEP of R20,318 per 440 mg vial, the cost of one course of treatment with 17 vials is R345,402 per patient.[55] (See Appendix A for details of the calculations.) This is a very large amount. At its current price, the cost of Herceptin required to treat a single patient is 4.1 times South Africa's Gross Domestic Product (GDP) per capita in 2018.[56] As discussed below, this implies that, at the current price, treatment with Herceptin is not cost-effective at commonly accepted thresholds for cost-effectiveness, despite its well-established efficacy and status as the standard of care.

25. Due to the high price of Herceptin, it is a major cost driver for medical aid schemes that cover it, even though HER2-positive breast cancer is far less prevalent than diseases such as diabetes and HIV. In schemes served by the pharmaceutical benefit manager Mediscor, Herceptin accounts for the third highest expenditure on any medicine, exceeded only by Novomix (an insulin used to treat diabetes) and Tribuss (an antiretroviral used to treat HIV).[57]

26. As mentioned, despite general recognition of the unique efficacy of trastuzumab for treating HER2-positive breast cancer and despite the fact that breast cancer is a Prescribed Minimum Benefit (PMB), the high price of Herceptin has severely limited access to treatment for patients covered by private health insurance. Trastuzumab is currently covered on affordable terms only by "upper end" medical aid schemes covering less than half of the less than 16% of the population who are privately insured.[58] Similarly, as mentioned, Dr. Abratt states that the cost of trastuzumab is the major factor responsible for the vast majority of patients with HER-positive breast

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[54] Abratt, Cost Considerations, p. 981.
[55] The total cost of treatment is, of course, even higher, since trastuzumab is, as discussed above, administered adjuvantly or neoadjuvantly with chemotherapy medicines, and the services of medical professionals, facilities, and equipment are also needed. However, the required chemotherapy medicines are available as generics and are therefore much less expensive than Herceptin and immediate drug costs are the largest cost factor in treatment of HER2-positive breast cancer (Abratt, Cost Considerations, p. 981). Thus, as mentioned, the cost of trastuzumab is "the major factor determining affordability" of treatment (Abratt, Response to Letter).
[56] South Africa's GDP in 2018 was R4,873,899,000 and its population was 57,752,600 (Statistics South Africa), which implies GDP per capita of R84,432 for the year. R345,402/R84,432 = 4.09.
[57] Mediscor *Medicines Review*: 2017, at p. 18.
[58] Dr. Georgia Demetriou, "The Landscape of Systemic Cancer Therapy in Africa," slide 11.

cancer who are covered by the less well-resourced medical scheme options in the private sector not having access to treatment with trastuzumab.[59] Dr. Jacques Snyman, a leading South African pharmaco-economist, estimates that only about 20% of patients currently covered by medical schemes who have HER2-positive breast cancer and should be receiving treatment with trastuzumab are currently receiving such treatment.

27. The South African Council of Medical Schemes (CMS) has recently proposed new draft guidelines for early and locally advanced breast cancer treatment as a PMB that include a recommendation for use of trastuzumab (given every three weeks) for one year in the adjuvant treatment of HER2-positive early-stage breast cancer.[60] The draft guidelines cite the National Department of Health's recommendation that, due to the high risk of micro-metastatic disease associated with HER2-positive tumours (even small, node-negative tumours), adjuvant trastuzumab-based therapy should be considered in all HER2-positive tumours.[61] However, the guidelines do not include a recommendation for use of trastuzumab to treat locally advanced breast cancer, and metastatic breast cancer is not addressed in these guidelines. We understand that this recommendation is currently under review. Undoubtedly, the cost of trastuzumab has had and will continue to have a significant impact on the effective scope of coverage of its use as a PMB.

B. Pricing, Access, and Utilisation in the Public Sector

28. Until very recently, trastuzumab was not available for treatment of the approximately 85% of South Africa's population who do not have private health insurance and therefore rely on the public sector.[62] As mentioned, trastuzumab was included on South Africa's essential medicines list (EML) for the treatment of early stage breast

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[59] Abratt, Response to Letter.
[60] Council for Medical Schemes, *Draft Prescribed Minimum Benefit definition guidelines for early and locally advanced breast cancer*, 26 March 2019 (CMS Draft breast cancer PMB), p. 18. In this document, early breast cancer is defined (citing a 2014 WHO reference) as disease confined to the breast with or without regional lymph node involvement and the absence of distant metastatic cancer (CMS Draft breast cancer PMB, p. 6).
[61] CMS Draft breast cancer PMB, p. 18.
[62] Cancer Alliance, *A2M Factsheet: Breast Cancer and HER2+ Breast Cancer, with a Look at Trastuzumab Access in South Africa*, August 2018 (Cancer Alliance Trastuzumab Factsheet), p. 17.

cancer June 2017. A tender for supply at public sector cancer treatment centres where breast cancer is treated was subsequently awarded[63] and we understand that, so far, modest volumes of trastuzumab have been purchased by some treatment centres.

29. With no trastuzumab biosimilars available, the public sector tender for trastuzumab was awarded to Roche-Genentech, the maker of Herceptin, for a more affordable version of Herceptin marketed under the trade name Herclon. The current public sector tender price of Herclon is R6,532 per 440 mg vial,[64] which implies a cost per patient of R111,037 for a one-year course of treatment using 17 vials.

30. The public sector price of Herclon is considerably less than the cost of Herceptin for the South African private sector but, as discussed below, remains above a level at which use of trastuzumab unambiguously satisfies accepted cost-effectiveness thresholds. As a result, cost continues to be an obstacle. Thus, for example, the Western Cape, which is relatively well-positioned to deliver treatment, has declined to implement the national public sector commitment to offer trastuzumab at its current price, stating: "The price was unaffordable and an unfunded mandate; the evidence furthermore showed an improved outcome in a small subset of patients with breast cancer. Should there be a significant price decrease, robust evidenced-based election criteria will be used in order to use trastuzumab for patients who will derive most clinical benefit."[65]

V. BIOSIMILAR COMPETITION WOULD GREATLY REDUCE THE COST OF TREATMENT

31. We understand that five suppliers – Mylan, Cipla, Amgen, Pfizer and Zydus – have applied to SAHPRA for registration of trastuzumab biosimilars, and that SAHPRA recently approved the applications submitted by Mylan. We commend SAHPRA for its action on Mylan's applications and urge prompt action on the outstanding applications. For the reasons discussed in the remainder of this memo, biosimilar

[63] Cancer Alliance Trastuzumab Factsheet, p. 17.
[64] DoH Master Procurement Catalog, March 15, 2019.
[65] Communication with the Western Cape Province Department of Health.

competition is critical to driving down the price of trastuzumab to a level at which all patients who need treatment with trastuzumab can get it.

32. The potential impact of biosimilar competition on the price of trastuzumab is most readily seen by comparing the public sector price of Herclon in South Africa, where the public sector could negotiate only with Roche-Genentech, and the public tender price of trastuzumab in India, where strong biosimilar competition exists.[66] Although, as mentioned, the South African public sector price of R6,532 per 440 mg vial of Herclon is considerably less than the SEP of R20,318 per 440 mg vial of Herceptin in the South African private sector, it is still 84% higher than the public sector tender price of R3,556 per vial in Tamil Nadu, India.[67]

33. These price differences are consistent with basic economic principles and an extensive body of international evidence and academic research. So far, the bulk of the data comes from the experience of small molecule pharmaceuticals, which have seen generic entry for hundreds of compounds in many countries over many years, rather than for biologics such as trastuzumab, for which biosimilar competition began much more recently. However, the consensus is that, provided steps are taken to educate healthcare providers and remove artificial barriers to substitution between biosimilars, strong price competition will develop between biosimilars as it has for small molecule generics.

34. When a product has no acceptable substitutes, economic principles teach that: the price will be determined by bargaining between the supplier and it customers; it will fall in a range between the minimum the supplier is willing to accept and the maximum a customer is willing to pay, which are determined by each party's next-best alternatives; and where the price falls in that range depends on the bargaining power of each party. In contrast, the closer products are as substitutes for one

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[66] For example, trastuzumab biosimilars from seven different manufacturers are listed as being available on the website 1mg.com, which reports retail prices for medicines in India (https://www.1mg.com/search/all?name=trastuzumab%20440mg).

[67] The current tender price per 440 mg vial of trastuzumab reported by the Tamil Nadu Medical Services Corporation is INR 16,998 (http://www.tnmsc.com/tnmsc/new/user_pages/drugtender.php?drugcat=sdg2017), which is about R3,556 at current exchange rates (Google exchange rate, May 2, 2019: ZAR 1 = INR 4.78). (R6,532/ R3,556) – 1 = 0.837.

another, the more strongly competition between suppliers will drive price down toward the incremental cost of supply. The more suppliers there are, the stronger this tendency, as it becomes more difficult for suppliers to collude, even tacitly. In actual marketplaces, downward pressure on prices tend to strengthen over time as suppliers respond to the competitive behavior of their rivals. Lastly, reductions in price typically lead, not only to savings for existing customers but also to an increase in the number of customers and the volumes that they purchase as products become more affordable, a phenomenon known as price-elasticity of demand.

35. Small molecule generics tend to provide textbook examples of these competitive dynamics, as pharmaceutical regulation provides for them to be certified as therapeutically equivalent to one another and supports substitution of generics for originator products and for one another by dispensing pharmacies. Competitive dynamics are not necessarily as strong for biologics such as trastuzumab, for which different manufacturers' products are, as the name "biosimilar" indicates, generally classified as therapeutically similar rather than equivalent and may not be substituted without a doctor's prescription to that effect. However, as discussed below, regulators, pharmaceutical benefit managers (PBMs), and physicians can drive strong competition between biosimilars and originator products and among biosimilars, and registration of multiple biosimilars is a prerequisite for pro-competitive policies to be effective.

36. Empirical research has long established that, as economic principles predict, the price of generic pharmaceuticals falls as the number of generic competitors increases. For example, the U.S. Food and Drug Administration, reporting average generic prices relative to originator prices for different numbers of generic entrants in 1999 – 2004, found that, whereas the first generic competitor prices its product only slightly lower, at 94% of the brand-name manufacturer's price, generic prices were 52% of originator prices when there were two generics, 33% of originator prices with 5 generics, and 20% to 26% with 6 to 10 generics.[68] Consistent with these data, Saha, *et al.* found in an

[68] U.S. Food and Drug Administration Center for Drug Evaluation and Research, "Generic Competition and Drug Prices," 2005.

econometric analysis of the U.S. pharmaceutical sales data that price reductions due to generic competition increase over time, and that each additional generic entrant caused the monthly rate of price decline to accelerate.[69] They also found and that price competition is particularly intense for "blockbuster" drugs,[70] of which trastuzumab is an example among biologic medicines. In an econometric analysis covering 10 different countries including Brazil, Mexico, the major E.U. markets, the U.S., Canada and Japan in 1998-2009, Danzon and Furukawa report that generic prices are negatively related to the number of generics, especially unbranded generics, in the marketplace.[71] Subject to variations due to institutional arrangements in some countries, this finding is consistent with previous studies of U.S. generic markets, which, Danzon and Furukawa state, "have consistently shown that generic prices decline with number of generic competitors."[72]

37. As mentioned, to date there has been less experience with biosimilar competition, and strong competition depends on policy measures as well as the number of approved biosimilars. However, a recent report by the pharmaceutical data analytics firm IQVIA on biosimilar competition in Europe, which has seen a relatively large number of biosimilars competing with originator biologics, shows that major reductions in prices can occur.[73] The report begins with two "Key Observations": first, that the entrance of biosimilars increases price competition; and second, that competition drives down price.[74] For example, "[i]n the case of [erythropoetins] in Portugal, the price decease for the total market including the originator product was -66%."[75]

38. The IQVIA report finds that, thus far, the reductions in prices of oncology medicines have been small but points out that the change in price per treatment day is

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[69] Atanu Saha, *et al.*, "Generic Competition in the US Pharmaceutical Industry," *Int. J. of the Economics of Business*, Vol. 13, No. 1, February 2006, pp. 15–38 (Saha, *et al.*) at p. 29.
[70] Saha, *et al.*
[71] Danzon, Patricia M., and Michael F. Furukawa, "Cross-national evidence on generic pharmaceuticals: pharmacy vs. physician-driven markets," National Bureau of Economic Research Working Paper No. 17226, 2011(Danzon and Furukawa, 2011), p. 21.
[72] Danzon and Furukawa, 2011, p. 21.
[73] IQVIA, *The Impact of Biosimilar Competition in Europe*, September 2018 ("IQVIA, Biosimilar Competition in Europe").
[74] IQVIA, Biosimilar Competition in Europe, p. 3.
[75] IQVIA, Biosimilar Competition in Europe, p. 3.

dependent on the length of time that biosimilars have been on the market, and that oncology biosimilars entered only in 2017.[76] The report also notes that, since the available data consist largely of list prices that do not account for non-published discounts, it understates the value of biosimilars.[77] However, for granulocyte colony-stimulating factor (GCSF),[78] for which rebate information was available, the report found that biosimilar discounts can be 80-90% off the originator list price and net prices are similar across the countries analysed.[79]

39. Another Key Observation in the IQVIA report is that biosimilars have the potential to improve patient access through lower prices, amongst other factors, *i.e.*, there is demand elasticity in the market.[80] This finding is important for a full consideration of the likely benefits of price reductions through trastuzumab biosimilar competition in South Africa, which will not only yield savings in the treatment of existing patients but, even more importantly, enable many more patients to be treated.

40. Norway has achieved dramatic reductions in price and improvements in access to biologics for patients through the use of a public tender process to drive biosimilar competition, together with strong financial incentives to health systems that switch to biosimilars and physician education about the batch-to-batch variability of biologics made by the same manufacturer and the fact that biosimilars are non-inferior to their reference drugs.[81] For example, the introduction of biosimilars of the Janssen Biotech IV injectable product Remicade (infliximab, used to treat rheumatoid arthritis and other autoimmune conditions) into Norway's public tender process in 2014 drove the price down 39% initially and 69% by 2015.[82]

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[76] IQVIA, Biosimilar Competition in Europe, p. 3.
[77] IQVIA, Biosimilar Competition in Europe, p. 3.
[78] One use of GCSF is to help white blood cells recover after chemotherapy (https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/g-csf).
[79] IQVIA, Biosimilar Competition in Europe, p. 5.
[80] IQVIA, Biosimilar Competition in Europe, pp 6 – 7.
[81] Kelly Davio, "Learning from the Norwegian Experience with Biosimilars," *The Center for Biosimilars*, November 15, 2017 (Davio, Norwegian experience; https://www.centerforbiosimilars.com/conferences/smi-2017/learning-from-the-norwegian-experience-with-biosimilars).
[82] "Biosimilars drastically reduced costs, expanded availability in Europe," *Healio Rheumatology*, April 28, 2018 (https://www.healio.com/rheumatology/rheumatoid-arthritis/news/online/%7B6d69b008-65d0-415b-a0f5-85c53bc8e4fc%7D/biosimilars-drastically-reduced-costs-expanded-availability-in-europe).

41. As the Norwegian example illustrates, active steps beyond simply approving biosimilars are required to strengthen and maximize the benefit of biosimilar competition. However, approval of multiple biosimilars is a critical requirement. In a comprehensive review of evidence regarding the requirements for competition among pharmaceuticals, economists Fiona Scott Morton and Lysle Boller conclude that, to reduce the prices of biologic medicines, "the single most valuable policy change in this area would be the approval of more biosimilars to compete with off-patent biologics."[83] Over time, as physicians become more familiar with biosimilars and clinical studies and experience demonstrate their non-inferiority to their reference drugs,[84] willingness to substitute biosimilars for originator products is likely to increase and generate intensified price competition.

42. Where separable higher and lower income markets exist for a medicine and a single seller exerts significant power over pricing, a possible alternative to biosimilar competition is tiered pricing, under which the seller charges correspondingly higher and lower prices for the medicine in these markets.[85] Currently, tiered pricing of trastuzumab is in effect in South Africa, with Roche-Genentech charging a high price for Herceptin to the private sector and a lower price for Herclon to the public sector. Moon, *et al.* (2011) compared tiered pricing with generic competition in developing countries and found that, based on "the past decade's experience with tiered pricing

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[83] Fiona Scott Morton and Lysle T. Boller, "Enabling Competition in Pharmaceutical Markets," Hutchins Center Working Paper #30, Yale School of Management, p. 35.

[84] See, for example: Davio, Norwegian experience; Sarah Jackson, "New Trastuzumab Biosimilar Approved by the FDA," *JNCCN 360 Breast Cancer*, June 17, 2019 (https://jnccn360.org/breast/news/trastuzumab-biosimilar-approved-by-the-fda-1/?email=d045f3013512b0a0d732acd1831e44d06ab5a9e3a8a73096a132972ce69eb3a4) reports that the clinical study that led to U.S. approval of Amgen's trastuzumab biosimilar Kanjinti established no clinically significant differences for existing Herceptin patients who switched to Kanjinti; Kelly Davio, "Real-World Evidence Shows Switching Among ESAs in CKD Is Not Associated With Risks to Safety, Efficacy," *The Center for Biosimilars*, June 24, 2019 (https://www.centerforbiosimilars.com/news/realworld-evidence-shows-switching-among-esas-in-ckd-is-not-associated-with-risks-to-safety-efficacy?utm_medium=email&utm_campaign=CFBSS%20Biosimilars%20enews%20-%206-29-19&utm_content=CFBSS%20Biosimilars%20enews%20-%206-29-19+CID_34dc9419141c9f93f38e005f9dca2a5c&utm_source=CM%20BioSim&utm_term=Real-World%20Evidence%20Shows%20Switching%20Among%20ESAs%20in%20CKD%20Is%20Not%20Associated%20With%20Risks%20to%20Safety%20Efficacy).

[85] Moon *et al.*, "A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries," *Globalization and Health*, 2011, 7:39 (Moon, *et al.*, http://www.globalizationandhealth.com/content/7/1/39), p. 1).

in HIV/AIDS, malaria, tuberculosis, visceral leishmaniasis and pneumococcal vaccines, … when markets were sizeable and multiple sources of production were available, tiered pricing performed poorly compared to competitive production in generating reliable and sustained price reductions."[86] Given the levels of expenditure on trastuzumab in South Africa and the number of manufacturers who have applied to register trastuzumab biosimilars, this finding applies to the present case, as can be seen by comparing Roche-Genentech's tiered prices of R20,318 per 440 mg vial for the South African private sector and R6,532 per vial for the public sector with the public sector price of R3,556 per vial under biosimilar competition in India.

43. The complexity of the landscape in which treatment with biologic medicines takes place, with regulators, manufacturers, pharmaceutical benefit managers, medical schemes, private and public healthcare providers, and patients all having important decision-making roles, makes it difficult to predict with any precision the magnitude of price reductions that trastuzumab biosimilar competition will bring about and the speed with which they will occur. However, the above review strongly supports the conclusion the approval of multiple biosimilars is a critical requirement for achieving more affordable pricing of trastuzumab, and the public sector price of R3,556 per 440 mg vial in India shows what is possible under biosimilar competition.

44. Even the current Indian public sector price of trastuzumab does not appear to be the "rock bottom" marginal cost of producing trastuzumab, as a recent article that reviews literature on the cost of manufacturing biologic medicines estimates that the Indian public sector price of trastuzumab is almost double the high end of a wide range of estimates of the cost of manufacturing monoclonal antibodies such as trastuzmab.[87] Further, the cost of manufacturing biologic medicines tends to fall over time as experience in manufacturing grows and technology advances.

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[86] Moon *et al.*, p. 8.

[87] Dzintars Gotham, "Cell line access to revolutionize the biosimilars market," *F1000Research* 2018, 7:537, last updated: 17 May 2019, reports $US 126 as the high end of the range of estimated costs of manufacturing (including capital investments in manufacturing facilities and overheads) 420 mg of trastuzumab (see Gotham, p. 2). At the $US/INR exchange rate of 0.015 used by Gotham to the Indian public sector price of INR 16,998 for 440 mg of trastuzumab implies a price of $US 243 for 420 mg of trastuzumab. $US 126 / $US 243 = 51.8%. (Gotham

45. Based on the above considerations, we use the Indian public sector price of R3,556 per 440 mg vial as a benchmark to estimate the cost savings and improvements in access to trastuzumab that are possible under biosimilar competition in South Africa. At this price, a course of treatment with trastuzumab would cost 17.5% of the current private sector price (an 82.5% saving) and 54.4% of the current public sector price (a 45.6% saving). Needless to say, these savings would represent a considerable improvement in affordability for South African medical schemes, the Department of Health, and patients.

VI. TRASTUZUMAB BIOSIMILAR COMPETITION WILL INCREASE ACCESS, SAVE AND EXTEND LIVES

46. Even more important than the reduction in costs at existing levels of utilisation of trastuzumab is the improvement in access to treatment that biosimilar competition will provide. If South Africa's private and public sectors simply maintained existing levels of spending on trastuzumab, they could dramatically improve access to treatment.

47. For the private sector, as mentioned, it is estimated that only about 20% of patients currently covered by medical schemes who have HER2-positive breast cancer and should be receiving treatment with trastuzumab are currently receiving such treatment. The Indian public sector price, being less than 20% of the current South African private sector price, indicates that it is possible for biosimilar competition to enable *all* patients covered by medical schemes who need treatment with trastuzumab to receive it without increasing private sector expenditure on trastuzumab.

48. For the public sector, the fact that the Indian public sector price is 45.4% less than the current South African public sector price indicates that it is possible for biosimilar competition to enable almost twice as many public sector patients who need treatment with trastuzumab to receive it without increasing public sector expenditure on trastuzumab.

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made a different price comparison, using an Indian biosimilar retail price, which is higher than the public sector price.)

49. Since so many patients who should be treated with trastuzumab are currently not receiving it in South Africa, expanding the numbers of patients treated at current levels of expenditure would obviously be justified. However, even doubling the number of patients treated would leave patients who rely on the public sector (*i.e.*, the great majority of patients) chronically underserved, since public sector utilisation of trastuzumab began only recently and remains very low. We therefore consider to what extent price reductions resulting from biosimilar competition could justify, not merely improving access at the current level of public sector expenditure on trastuzumab, but also increasing expenditure to expand access while taking into account the budget constraints of the public sector.

A. Price Reduction Is Critical for Access to Trastuzumab to be Expanded Based on Cost Effectiveness

1. QALYs as a Cost Effectiveness Measure for Trastuzumab

50. To allocate limited healthcare budgets among the vast array of possible uses, decisions must be made, explicitly or implicitly, as to which expenditures will deliver sufficient benefit to justify the cost. To allow decision-making to be based on explicit criteria, a variety of measures of the benefits of healthcare – for example, Number Needed to Treat, Disability Adjusted Life Years (DALYs), and Quality Adjusted Life Years (QALYs) – have been developed. Typically, for any given medical treatment, an estimate of its benefit based on one these measures is divided by its cost to get an Incremental Cost-Effectiveness Ratio (ICER) for that treatment. The estimated ICER for the treatment is then compared with a benchmark ICER that serves as a cut-off for deciding whether the treatment should be funded. If the ICER for the treatment falls below the cutoff, the required expenditure is considered to be justified; if the ICER for the treatment exceeds the cutoff, it is not.

51. All measures of the benefits of healthcare and ICER cut-offs involve a good deal of judgment and are subject to ongoing discussion and even controversy.[88] However, if

[88] See, for example: Samy Suissa, "The Number Needed to Treat: 25 Years of Trials and Tribulations in Clinical Research," *Rambam Maimonides Medical Journal*, July 2015, Volume 6, Issue 3, e0033; Lisa A. Robinson, *et al.*,

a treatment scores well enough based on a commonly used measure of benefit and a conservatively low ICER cut-off, expenditure on the treatment is likely to be viewed as justified. The purpose of the present consideration is thus to assess whether biosimilar competition could drive the price of trastuzumab low enough for increased public sector expenditure on this medicine to be generally accepted.

52. The QALY is a widely used measure of the health benefit that a medicine provides, which was used by the South African Department of Health in deciding whether to add trastuzumab to South Africa's Essential Medicines List.[89] A QALY is the estimated increase in years of life remaining for a patient following a treatment, where each year is weighted with a quality-of-life score (on a 0 to 1 scale), so that one QALY is equal to one year of life in perfect health.[90] In estimating QALYs, the quality of life is often measured in terms of a patient's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.[91] The QALY metric thus seeks to account for a range of possible outcomes of treatment rather than a single outcome such as survival over a certain period.

53. South Africa's National Essential Medicine List Review of trastuzumab in 2016 – 2017 states that the QALY-based threshold for affordability of medicines "is often quoted as 1 - 3 times [Gross] Domestic Product (GDP) [per capita], with developing countries usually using not more than 1 times GDP [per capita]."[92] That is, the review stated that in developing countries a medicine is often not considered cost effective if its ICER measured by its cost per QALY exceeds the country's GDP per capita. Based on this criterion, the review warned, as mentioned, that trastuzumab may well be deemed not cost-effective at the current offered price.[93]

"Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds," *Health Policy and Planning*, 32, 2017, 141–145.

[89] National EML Review of trastuzumab, pp. 10 – 11.

[90] https://www.nice.org.uk/glossary?letter=q.

[91] https://www.nice.org.uk/glossary?letter=q.

[92] National EML Review of trastuzumab, p 10.

[93] National EML Review of trastuzumab, p 11.

54. The criterion used in the EML review of trastuzumab is consistent with relevant literature. For example, Gershon *et al.*, who use QALYs to measure the benefits of trastuzumab, state that

> In LMICs [(Low to Middle Income Countries], the threshold suggested by the World Health Organization (WHO) is related to the annual gross domestic product (GDP) per capita of each country. If the ICER of the intervention is less than 1× GDP per capita, the intervention is considered as very cost-effective. If the ICER is between 1 and 3× GDP per capita, the intervention is considered cost-effective. Otherwise, it is considered not cost-effective. … the use of a figure close to the GDP per capita as a cost-effectiveness threshold is widespread in many countries.[94]

Gershon *et al.* also report that QALY is used to address diseases such as cancer and for interventions that evaluate pharmaceuticals.[95]

55. In an investment case for an action plan to prevent and treat Hepatitis B and C in South Africa on which DoH personnel were coauthors, Hecht, *et al.* state:

> To interpret cost-effectiveness and set thresholds for investment decisions, we expressed the incremental cost-effectiveness ratios (ICERs) as a percentage of per capita GDP. While no definitive cost-effective threshold exists for South Africa, recent work suggests that estimates of less than half of per capita GDP are likely to represent good value. Other recent work focusing on the consumption value of health benefits suggests a somewhat higher threshold around 1-2 times per capita GDP.[96]

2. Achievement of Cost Effectiveness through Price Reduction

56. With this background on QALYs as a cost effectiveness measure for trastuzumab in mind, we assess the current cost effectiveness measure of trastuzumab and the role

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[94] Gershon *et al.*, p. 2.
[95] Gershon *et al.*, p. 2.
[96] Robert Hecht, *et al.*, "The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up," *Health Policy and Planning*, 33, 2018, 528–538 at p. 531. Consistent with their focus on communicable diseases, Hecht, *et al.* use as their measure of benefit DALYs, which are similar to QALYs but can yield different conclusions in some cases.

biosimilar competition could play in making trastuzumab, especially in the public sector.

57. For this analysis, we use the estimate by Gershon *et al.* that a one-year course of trastuzumab yields a gain of 1.02 QALYs in South Africa, the current private sector price of a 440 mg vial of Herceptin and current public sector price of Herclon in South Africa, the public sector price of trastuzumab in Tamil Nadu, India, and South African GDP and population figures for 2018 from Statistics SA, and assume 17 vials per course of treatment, as before. Using these data, we compute ICERs (ZAR per QALY) at the three different prices and divide them by GDP per capita in order to compare the ICERs with the possible cut-offs for health care expenditure discussed above. This analysis yields the following results:

- At the current South African private sector price, the ratio of ICER to GDP per capita for trastuzumab is 4.01;
- At the current South African public sector price, the ratio of ICER to GDP per capita for trastuzumab is 1.29;
- At the current Indian public sector price, the ratio of ICER to GDP per capita for trastuzumab is 0.70.[97]

58. These results indicate that:

- At the current South African private sector price, trastuzumab does not satisfy WHO cost-effectiveness criteria for LMICs, which identify a range of 1 to 3 for the ratio of ICER to GDP per capita;
- At the current South African public sector price, trastuzumab falls within the WHO cost-effectiveness range for LMICs, but may be found not cost effective based on the ICER to GDP per capita ratio of 1 identified in the EML Review for trastuzumab as the usual cutoff for developing countries;
- At the current Indian public sector price, trastuzumab may not satisfy the strictest ICER to GDP per capita ratio of 0.5 proposed in academic literature but falls well within the range below 1 identified in the EML Review for trastuzumab as usual for developing countries and characterized by Gershon, *et al.* as "very cost-effective."

59. In sum, these results, combined with the review of pharmaceutical and biosimilar competition above, strongly indicate that the current tiered pricing arrangement is

[97] See Appendix A for the calculations.

inadequate to allow full access to trastuzumab for breast cancer patients who need it, and that full access can likely be achieved only through vigourous competition among multiple trastuzumab biosimilars.

VII. THE IMPORTANCE OF PROMPTLY REGISTERING ALL QUALIFIED BIOSIMILARS

A. The Need for Registration Is Now the Critical Barrier for Trastuzumab Biosimilars

60. We understand that Mylan, whose trastuzumab biosimilar has now been approved by SAHPRA, received a global licence from Roche-Genentech that allows it to market its trastuzumab product in South Africa. The global license was granted as part of a settlement agreement in which Mylan agreed to withdraw its legal challenges on Roche's U.S. held trastuzumab patents.[98]

61. Regarding the possibility of intellectual property barriers to the other trastuzumab biosimilar applicants, we understand that the main patents that protected Herceptin have expired, but that Roche-Genentech has been granted other, secondary patents in South Africa which remain in effect despite almost all of them having been withdrawn or revoked in Europe.[99] Roche-Genentech has not stated whether it will not seek to block additional competitor products from entering the market through asserting secondary patent claims in South Africa.[100]

62. Since the trastuzumab biosimilar applicants who have not yet received approval have continued to pursue registration in South Africa despite uncertainty over whether Roche-Genentech intends to assert any of its remaining patents, which are likely vulnerable to challenge given their history in Europe, it is critical that the applicants be approved promptly to bring this uncertainty to an end and to allow challenges to the remaining patents to be undertaken if needed.

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[98] See Cancer Alliance Trastuzumab Factsheet, p. 26.
[99] See Cancer Alliance Trastuzumab Factsheet, p. 25. We have obtained our understanding that the main patents that protected Herceptin have expired since preparing the Cancer Alliance Trastuzumab Factsheet.
[100] See Cancer Alliance Trastuzumab Factsheet, p. 26.

B. It Is Important to Register All Qualified Biosimilars

63. It is important that all the trastuzumab biosimilars for which applicants have satisfied the regulatory requirements be registered promptly because, as shown above based on international evidence, the price of biosimilars is greatly affected by the number of entrants and a single generic entrant typically prices its product close to the originator.

64. In South Africa, the lack of price competition when there is only one generic or biosimilar is illustrated by the Single Exit Price for Filgrastim Teva, a biosimilar version of AmGen's product Neupogen (filgrastim), which is to our knowledge the first and only biosimilar approved before Mylan's trastuzumab.[101] The SEP for Filgrastim Teva is only 10% to 12.5% less than that of its reference medicine, Neupogen.[102]

65. Regarding trastuzumab specifically, it should not be expected that Roche-Genentech will compete vigourously on price with Mylan's recently approved biosimilar, since Roche-Genentech has introduced a formulation of Herceptin for subcutaneous rather than IV injection. This creates an incentive for Roche-Genentech to promote the convenience benefits of its subcutaneous formulation and not to drive down the price of trastuzumab for IV injection, as a lower price for the IV formulation would discourage switching to the originator's proprietary subcutaneous formulation. Relevant examples of originators' strategies are presented in the IQVIA report on biosimilar competition in Europe discussed above. The report describes how Roche-Genentech responded to prospect of the entry of biosimilars of the IV version of its oncology medicine Mabthera (rituximab) by starting to switch patients to its subcutaneous version of Mabthera before the biosimilar launch.[103] The report also describes a similar strategy by Amgen, the maker of Neupogen (of which Filgrastim Teva is the biosimilar version in South Africa, as discussed above), which introduced Neulasta (pegfilgrastim) a long-acting version of filgrastim.[104]

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[101] Cipla South Africa, "South Africa's first biosimilar oncology drug authorised for use," *BizCommunity* (https://www.bizcommunity.com), 3 August 2018.
[102] Calculation based on SEP data in the Database of Medicine Prices. 21st December 2018.
[103] IQVIA, Biosimilar Competition in Europe, p. 11.
[104] IQVIA, Biosimilar Competition in Europe, pp. 11-12.

66. Adding to the importance of registering promptly all qualified trastuzumab biosimilars is that, historically, not all applicants whose generic products are registered in South Africa ultimately decide to launch their products.[105] Thus it cannot be assumed that the benefits of having a given number of trastuzumab biosimilars competing in South Africa will be realized by registering only that number of biosimilars.

67. An additional benefit of registering all qualified biosimilars is that they could ensure a reliable and affordable supply that does not depend exclusively on the originator who, as mentioned, now has a greater interest in promoting its subcutaneously injectable trastuzumab product, for which it retains exclusivity. Even if a biosimilar were not to enter immediately upon being registered, it would have an incentive to do so in the event of a supply disruption and would be able to enter much more quickly if it were already registered.

C. Failure to Register Will Substantially Delay Biosimilar Entry

68. We understand that it will take the biosimilar manufacturers six to seven months to set up distribution of their products. We understand also that they will not commence this process until their products have been approved. Six to seven months must therefore be added to any additional time taken for SAHPRA to register the four remaining trastuzumab biosimilars for which applications have been submitted.

69. Since, as discussed, the magnitude of trastuzumab price reductions will depend on the number of competing biosimilars and will take time to unfold, delay in approving any of the remaining applicants will postpone realization of the full benefits of biosimilar price competition.

D. The Benefits of Registering Trastuzumab Biosimilars Will Increase Greatly over Time

70. As mentioned, rates of breast cancer diagnosis are increasing and the public sector is in the early stages of making treatment with trastuzumab available at treatment centres. The benefits of price reduction through biosimilar competition, which are

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[105] H M J Leng, A M Pollock, D Sanders, "The impact of the Medicines Control Council backlog and fast-track review system on access to innovative and new generic and biosimilar medicines of public health importance in South Africa," *South African Medical Journal*, April 2016, Vol. 106, No. 4, 350 – 353 at 350.

already large given the existing patient population and expenditures on trastuzumab, will increase greatly in the coming years.

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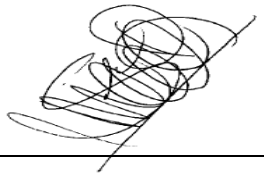
Submitted:



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