

IN THE COMPETITION COMMISSION OF SOUTH AFRICA

In the complaint submitted by:

TREATMENT ACTION CAMPAIGN

Concerning the conduct of:

MSD (PTY) LTD

MERCK & CO., INC. AND RELATED COMPANIES

STATEMENT OF COMPLAINT

THE COMPLAINANT

1. The complainant is the **TREATMENT ACTION CAMPAIGN** (“the TAC”), an association incorporated under section 21 of the Companies Act 61 of 1973 with its head office at 34 Main Road, Muizenberg, Cape Town.
2. As set out in its Constitution, the objectives of the TAC include (but are not limited to) –
 - a) Campaigning for equitable access to affordable treatment for all people with HIV/AIDS;
 - b) Challenging by means of litigation, lobbying, advocacy and all forms of legitimate social mobilisation, any barrier or obstacle that limits access to treatment for HIV/AIDS in the private and public sector; and
 - c) Campaigning for access to affordable and quality health care for all.
3. Further detail on the TAC – including its work regarding access to medicines in general and antiretroviral (“ARV”) medicines in particular – is set out in the affidavit of Abdurrazack “Zackie” Achmat, the organization’s chairperson and a person living openly with HIV. Achmat’s affidavit – attached marked **Annexure TAC** – also sets out the TAC’s previous interactions with the Competition Commission (“the Commission”). In

particular, it details the TAC's role in the 2002 complaint brought by Hazel Tau and others against the GlaxoSmithKline ("GSK") and Boehringer Ingelheim ("BI") groups of companies in case number 2002Sep226 ("the *Tau* case").

THE SUBJECTS OF THE COMPLAINT

4. The first subject of the complaint is **MSD (PTY) LTD** ("MSD"), a company duly incorporated under the laws of South Africa and with its registered office at 117 16th Road, Halfway House. MSD is cited because to the best of the complainant's knowledge it has and exercises the exclusive right – subject to its licensing agreements with Aspen Pharmacare Holdings Limited ("Aspen") and Adcock Ingram Limited ("Adcock") – to market and sell the ARV medicine efavirenz ("EFV") in South Africa (branded as Stocrin®), as the South African representative of Merck & Co., Inc.
5. The complaint is also submitted against **MERCK & CO., INC.** ("Merck"), a research-based pharmaceutical company with headquarters at One Merck Drive, Whitehouse Station, NJ 08889-0100, USA, and/or those companies that are related to it and have the right to market and/or sell Efv to any entity in South Africa (including MSD). As the complainant has been unable to ascertain which particular companies related to Merck have the right to sell and market Efv to or in South Africa, it requests that the Commission obtain this information during the course of its investigations.
6. For convenience, MSD and Merck – as well as any companies that are related to Merck and have the right to market and/or sell Efv to any entity in South Africa (including MSD) – are referred to collectively as the respondents.
7. Efv is claimed per se in South African Patent No. 93/5724, which is currently in force and will expire in the normal course on 6 August 2013. As at July 2007, Merck was registered as the relevant patentee, with its address for service under section 87 of the Patents Act 57 of 1978 being DM Kisch Inc., 54 Wierda Road West, Wierda Valley, Sandton.

8. The invention of South African Patent No. 93/5724 also covers pharmaceutical compositions containing EFV; its use in the treatment of HIV/AIDS; its use in combination with the ARV medicines zidovudine (“AZT”), didanosine (“ddI”) and zalcitabine (“ddC”); and a process for synthesizing EFV.
9. There is a further South African patent that covers combinations of EFV and other ARV medicines. As at July 2007, Gilead Sciences Inc. (“Gilead”) – a research-based pharmaceutical company with headquarters at 333 Lakeside Drive, Foster City, CA 94404, USA – was registered as the patentee of South African Patent No. 2005/05852, with its address for service under section 87 of the Patents Act 57 of 1978 being Bowman Gilfillan Attorneys, 165 West Street, Sandton.
10. South African Patent No. 2005/05852, which is in force and will expire in the normal course on 13 January 2024, covers the use of the combination of the ARV medicines tenofovir disoproxil fumarate (“TDF”) and emtricitabine (“FTC”) as anti-HIV therapy. Of relevance to this complaint is that the patent also claims the combination of TDF, FTC and EFV, and an oral pharmaceutical dosage form comprising TDF, FTC and EFV.
11. However, Gilead has expressly committed itself not to enforce whatever HIV-related patents it holds in the 95 developing countries (including South Africa) eligible for its “no-profit pricing”. In addition, Merck has the exclusive right to market TDF/FTC/EFV in South Africa. In terms of an agreement between Gilead and Merck, “Gilead will manufacture ATRIPLA using efavirenz supplied by Merck ... [which] in turn will handle distribution of the product in the countries covered by the agreement”. This is set out in a press release dated 11 August 2006, which is available online at http://www.gilead.ca/wt/sec/pr_895234 and is attached marked **Annexure MSD1**.

THE ESSENCE OF THE COMPLAINT

12. The complainant alleges that the respondents have violated section 8(c) of the Competition Act 89 of 1998 (“the Act”) by refusing to license –

- a) Any existing company in South Africa (other than Aspen and Adcock) to import into, manufacture, use, offer to dispose of and/or dispose of in South Africa, generic EFV products; and
 - b) Any existing company in South Africa (including Aspen and Adcock) to import into, manufacture, use, offer to dispose of and/or dispose of in South Africa, co-formulated and/or co-packaged generic products containing EFV and at least one other ARV medicine.
13. Although MSD claims that it is “currently assessing additional requests for a license to manufacture and distribute efavirenz in South Africa” (**Annexure JMB20**, which is attached to Jonathan Berger’s affidavit marked **Annexure JMB**), it has already refused to license at least two existing companies in South Africa:
- a) In a letter to Cipla-Medpro (Pty) Ltd (“Cipla-Medpro”) dated 9 May 2006, MSD’s former Chief Executive Officer (“CEO”) explained his company’s decision not to license Cipla-Medpro:

As I previously advised, Merck & Co considers each request for a license seriously. We evaluate such requests based on a thorough assessment of the demand for Efavirenz in South Africa in South Africa as well as other criteria which were previously communicated to Cipla We are monitoring the demand for Stocrin both in public and private sectors, and have concluded that at this stage MSD SA is in position to adequately meet all of the demand for this product. In addition, we expect Aspen, another supplier, will be in a position to come to market in a few months to ensure multiple supplies for this medicine. (**Annexure MSD2**)
 - b) More recently, Cipla-Medpro was once again effectively denied a licence. In a letter dated 25 September 2007, MSD’s new CEO sought to justify his company’s position as follows:

Given that the granting of the second efavirenz licence occurred only recently at the end of August 2007, further applications for efavirenz licences will be evaluated and the due process will be followed *once a clearer understanding of the supply of efavirenz has been established.* (**Annexure MSD3**, emphasis added)

- c) The complainant has reliably been advised that MSD has also refused to license Sonke Pharmaceuticals (Pty) Ltd, a joint venture between Ranbaxy (SA) (Pty) Ltd and Community Investment Holdings (Pty) Ltd.
14. Regarding MSD's effective refusal to license, a letter (dated 4 June 2007) sent by the complainant's legal representatives – the AIDS Law Project ("ALP") — to which MSD has yet to reply, records as follows:
- 2. While we appreciate your timely response, we do not believe that you have addressed the key issues raised in our letter dated 21 May 2007. In particular, you have not committed MSD to –
 - a. Licensing additional generic companies to supply the South African and SADC [Southern African Development Community] markets on reasonable terms; and
 - b. Permitting Aspen to bring co-formulated and/or co-packaged generic products containing EFV and at least one other ARV medicine to market.
 - 3. Instead, you have simply –
 - a. Asserted that you "are currently assessing additional requests for a license to manufacture and distribute efavirenz in South Africa", without committing to issuing licences should the prospective licensees be able to satisfy your concerns relating to certain objective criteria – "[i]ssues of bioequivalence, safety, quality, forecasting and planning"; and
 - b. Postponed any decision relating to licences in respect of fixed-dose combination (FDC) products containing EFV, further claiming that the MCC does not permit co-packaging (more on this below).
- The ALP letter is attached to Berger's affidavit as **Annexure JMB21**.
15. As already indicated, MSD has subsequently granted a second licence – apparently on substantially similar (if not the same) terms as the Aspen licence – to Adcock. The award of that licence, which is similarly restricted to stand-alone EFV products, is

addressed in a 7 September 2007 press release attached marked **Annexure MSD4** and available online at <http://www.adcock.com/article.aspx?ArticleId=43>.

16. By refusing to license further existing companies in South Africa, and by refusing to permit Aspen and Adcock to bring co-formulated and/or co-packaged generic products containing EFV and at least one other ARV medicine to market, the respondents have – without good cause – collectively threatened access to comprehensive treatment for HIV/AIDS in both public and private sectors by –
 - a) preventing the market entry in South Africa of significantly cheaper generic EFV products;
 - b) preventing the market entry in South Africa of a range of co-formulated and/or co-packaged products containing EFV; and
 - c) placing the sustainability of supply of EFV products in South Africa under threat.

STRUCTURE OF THIS STATEMENT OF COMPLAINT

17. This statement of complaint addresses the following two factual issues:

- a) The extent, nature and treatment of HIV infection in South Africa; and
 - b) The implications of the respondents' refusal to license.

The legal arguments made in support of this statement of complaint are set out in a separate document entitled **LEGAL SUBMISSIONS**.

18. The statement of complaint first addresses the following in relation to the extent, nature and treatment of HIV infection in South Africa:
 - a) State of the HIV/AIDS epidemic in South Africa; and
 - b) Treating HIV infection with highly active ARV therapy ("HAART").

19. The statement then addresses the implications of the respondents' refusal to license, in relation to –

- a. the exclusion of significantly cheaper generic EFV products from the South African market;
- b. the exclusion of a range of co-formulated and/or co-packaged ARV products from the South African market; and
- c. threats to the sustainability of supply.

EXTENT, NATURE AND TREATMENT OF HIV INFECTION IN SOUTH AFRICA

State of the HIV/AIDS epidemic in South Africa

20. Because of its extent, nature and impact, HIV/AIDS represents the “greatest threat to public health in our country” and “the most important challenge facing South Africa since the birth of our new democracy”. (*Minister of Health v Treatment Action Campaign (No 2) 2002 (5) SA 721 (CC)* at paragraphs 93 and 1 respectively). The impact of the epidemic is discussed in frank terms in the report *A Nation in the Making – A discussion document on macro-social trends in South Africa*, published by the Presidency in 2006 and available online at <http://www.info.gov.za/otherdocs/2006/socioreport.pdf>:

[T]here is clearly not only a pandemic in silent attack, but its fatal impact is starting to express itself palpably in both morbidity and mortality. The most affected in this regard are able-bodied citizens in the prime of their lives. These would most likely be parents of young children and possibly breadwinners of extended families who are also among the most skilled within the population (at page 65).

21. Despite this reality, government was for some time reluctant to act with the urgency and commitment demanded by the epidemic. Finally, after many years of conflict with civil society, strong political leadership from Deputy President Phumzile Mlambo-Ngcuka and former Deputy Minister of Health Nozizwe Madlala-Routledge led to the adoption of the new national *HIV & AIDS and STI Strategic Plan for South Africa 2007-2011* (“the NSP”) in 2007 – endorsed by the South African National AIDS Council (“SANAC”) on 30 April

2007 and thereafter approved by Cabinet on 2 May 2007. A copy of the executive summary of the NSP is attached marked **Annexure MSD5**. The complete document will be made available upon request.

22. All key stakeholders, including government's most vociferous critics in civil society, were integrally involved in the NSP's conceptualisation, development and finalisation. Importantly, the NSP affirms the necessity of dealing decisively, comprehensively and urgently with the epidemic, noting as follows (at page 17):

HIV and AIDS is one of the major challenges facing South Africa today. Some two decades since the introduction of this disease in the general population, the epidemiological situation is characterized by very large numbers of people living with HIV and a disproportionate effect on particular sectors of society, viz.: young women, the poor, as well as those living in underdeveloped areas in the country. HIV and AIDS, however, affect the lives of all people who live in South Africa in different ways.

23. The primary aims of the NSP are to reduce the rate of new HIV infections by 50% by 2011; and to reduce the impact of HIV/AIDS by expanding access to appropriate treatment, care and support to 80% of those in need by 2011. The four priority areas of the NSP are prevention; treatment, care and support; research, monitoring and surveillance; and human rights and access to justice. They collectively identify a range of activities, targets and programmes required to ensure that the NSP's aims are realised.
24. As an evidence-based plan, the NSP places much reliance on the report *Demographic Impact of HIV/AIDS in South Africa* ("Demographic Impact"), the most comprehensive analysis of the extent and impact of the South African epidemic yet undertaken. A copy of the Executive Summary of *Demographic Impact* is attached marked **Annexure MSD6**. The full report, which will be made available upon request, is available online at <http://www.assa.org.za/aids/content.asp?id=1000000449>.
25. *Demographic Impact* makes use of the ASSA2003 AIDS and Demographic model, which in turn "is based on a thorough analysis of a range of epidemiological and demographic

data including the antenatal surveys and recorded deaths up to the year 2003. In addition the projections allow for the impact of major current interventions.” (Page i)

26. In his expert affidavit (**Annexure LJ**), the University of Cape Town’s Leigh Johnson – one of the authors of *Demographic Impact* – makes use of the ASSA2003 AIDS and Demographic model to consider the impact of the HIV/AIDS epidemic and its implications for the provision of ARV treatment in accordance with the targets and timeframes set out in the NSP. On projections regarding mortality and life expectancy in particular, Johnson comes to the following conclusions (at paragraphs 29 – 32):

As a result of the low rates of access to treatment and the high numbers of people sick with AIDS, South Africa is experiencing high levels of AIDS mortality. It is estimated that during 2006, approximately 350,000 people died from AIDS. This has led to a reduction in life expectancy at birth, from approximately 63 years in 1990, to approximately 51 years in 2006.

...

If the mortality rates experienced in 2006 were to continue in future, roughly 56% of current 15-year olds would die before reaching the age of 60. The proportion would be 29% if mortality rates continued at levels experienced in 1990. ...

AIDS has thus led to massive increases in mortality rates, particularly in the economically active ages. ...

As a result of the rapid increase in adult mortality levels, there has been a dramatic rise in numbers of orphaned children. The number of children under the age of 18 who have lost both parents is estimated at 430,000 as at mid-2006. A further 1.1 million have lost their mother, and another 2.4 million have lost their father. Equivalently, 2.4% of children have lost both parents, a further 6% have lost their mother, and another 13% have lost their father.

Treating HIV infection with HAART

27. HIV/AIDS can be treated effectively by ensuring access to ARV medicines, which specifically target HIV infection itself rather than AIDS-related opportunistic infections. These drugs are combined in various different treatment regimens that collectively are known as HAART. In this statement of complaint, which draws heavily on Dr Robin

Wood's expert affidavit (attached marked **Annexure RW**), HAART and ARV treatment are used interchangeably.

28. HAART has revolutionised the management of HIV infection, resulting in a radical reduction in mortality and morbidity figures amongst groups with access to treatment. Additional health benefits include the reduction and/or elimination of opportunistic infections, the restoration of immune function, and a reduction in infectiousness. With access to HAART, people with HIV/AIDS are able to lead longer and healthier lives. Access to ARV treatment thus directly results in an improved quality of life and the restoration of dignity, allowing people with HIV/AIDS who were previously ill to resume ordinary everyday activities, such as work.
29. Since 1996, HAART has been the standard of care in Europe, North America and Brazil. Scientific consensus confirms that at least three drugs should be used together to ensure maximum clinical efficacy, reduce side effects and limit the emergence of resistant strains of the virus. The simultaneous use of three or more drugs, including drugs from different therapeutic classes, is essential for individual clinical outcomes and for public health protection. In short, it is necessary to have access to a combination of drug choices both within and between drug classes.
30. ARV medicines target either a particular step in the life cycle of HIV or its interaction with host cells. The ARV medicines in general use in South Africa inhibit one of two key viral enzymes required by HIV for replication – reverse transcriptase (essential for the completion of the early stages of viral replication) or protease (required for the assembly and maturation of new HIV) – and can be divided into the following therapeutic classes:
 - a) Nucleoside analogue reverse transcriptase inhibitors (“NRTIs”): AZT, lamivudine (“3TC”), FTC, abacavir (“ABC”), stavudine (“d4T”) and ddI;
 - b) Nucleotide analogue reverse transcriptase inhibitors (“NtRTIs”): TDF;
 - c) Non-nucleoside reverse transcriptase inhibitors (“NNRTIs”): nevirapine (“NVP”) and EFV;

- d) Protease inhibitors (“PIs”): lopinavir (“LPV”), ritonavir (“RTV”), indinavir (“IDV”), saquinavir (“SQV”) and atazanavir (“ATZ”).
31. Some ARV medicines are available in fixed-dose combination form. LPV/r is the only form in which LPV is manufactured internationally. In South Africa, the only combinations currently available other than LPV/r are TDF/FTC, AZT/3TC, 3TC/ABC, AZT/3TC/ABC and d4T/3TC/NVP. TDF/FTC is the only form in which FTC is marketed in South Africa, although it is available as a stand-alone product outside of the country.
32. There is a range of other ARV medicines – such as fosamprenavir, tipranavir, enfuvirtide, darunavir, raltegravir and maraviroc – that are available elsewhere but have yet to be registered for use in South Africa. Certain combinations of ARV medicines – such as AZT/3TC/NVP, TDF/FTC/EFV, TDF/3TC/EFV and d4T/3TC – are available for use in countries other than South Africa. A few ARV medicines – such as amprenavir and zalcitabine (“ddC”) – are no longer available for use anywhere. In addition, all stock of one ARV medicine – nelfinavir (“NFV”) – was recently recalled as a result of product contamination.
33. The ability to devise different drug regimens allows practitioners to take into account problems such as proven antagonism between specific drugs, potency and side effect profile, potential for maintenance of future treatment options, pregnancy, potential for primary acquisition of resistant viral strains, the incidence of tuberculosis (“TB”) and hepatitis B and/or C, amongst other factors. All these factors have an influence on what drug regimen is selected.
34. In the public sector, however, only a limited number of these ARV medicines (AZT, 3TC, ABC, d4T, ddI, NVP, EFV, LPV/r and RTV) are available for treating HIV infection. The National ARV Treatment Guideline, to which Wood’s expert affidavit refers, details the standard treatment regimens that govern the provision of HAART in the public sector. These regimens are discussed in more detail in Wood’s affidavit.

35. The availability of a number of ARV medicines in a particular therapeutic class does not necessarily mean that people with HIV/AIDS have a choice of products. The science of HIV treatment shows that ARV medicines are generally not interchangeable. Numerous factors combine to limit or completely exclude treatment combinations and options. The implications of this are addressed in the legal submissions, most importantly in relation to market definition and the establishment of dominance.

IMPLICATIONS OF THE RESPONDENTS' REFUSAL TO LICENSE

36. Directly and through its legal representative, the complainant has engaged with the respondents over many years regarding the need for them to license manufacturers and/or importers of generic EFV medicines on reasonable and non-discriminatory terms. Notwithstanding this engagement, the detail of which is set out in Berger's affidavit, the respondents' conduct continues to give rise to the following three problematic outcomes:

- a) The exclusion of significantly cheaper generic EFV products from the South African market;
- b) The exclusion of a range of co-formulated and/or co-packaged ARV products from the South African market; and
- c) Threats to the sustainability of supply.

These three matters are now addressed in turn.

Exclusion of cheaper generic EFV products from the market

37. Whilst the complainant does not allege that the respondents are engaged in prohibited excessive pricing, it is nevertheless concerned about the impact – or potential impact – of the respondents' conduct on the pricing of EFV products respectively. Importantly, the respondents claim that they are selling the relevant ARV medicines in South Africa at cost. In other words, they claim to be making no profit on domestic sales of these products. In particular, MSD claims that "STOCRIN [EFV] is already provided in South

Africa at prices from which MSD does not profit." (**Annexure JMB20** to Berger's affidavit)

38. The question, therefore, is not whether the respondents are able to bring the relevant EFV products to market at lower prices, but rather whether the Act entitles them to prevent generic companies from entering the market in these circumstances, namely where such conduct:
 - a) will have little to no impact on the respondents' profit margins;
 - b) excludes cheaper generic products from the market; and
 - c) results in threatening access to comprehensive treatment for HIV/AIDS in both public and private sectors.

This issue is addressed in the legal submissions.

Pricing of EFV products

39. MSD markets stand-alone EFV products in South Africa at its best international prices, which are offered to both the public and private sectors:
 - a) EFV 200mg – US\$394.20 per adult per year; and
 - b) EFV 600mg – US\$237.25 per adult per year (**Annexure MSD7**).
40. In addition, it has committed to pricing TDF/FTC/EFV at US\$613.20 per adult per year in developing countries such as South Africa (**Annexure MSD7**). To date, however, the combination has yet to be registered here. It is therefore not generally available for sale in the country
41. MSD's prices – which appear to be determined by Merck – are significantly cheaper today than they were at the beginning of the decade. Interestingly, Merck first announced a substantial reduction in the price of EFV (200mg capsules) in March 2001 (**Annexure MSD8**), only days after the complainant had been admitted as *amicus curiae*

by the Transvaal High Court in the case of *Pharmaceutical Manufacturers' Association and Others v Government of the Republic of South Africa and Others* (case no: 4183/98). At the same time, Merck also reduced the price of IDV. Reuters reported that “[t]he new prices represented reductions of some 40 to 50 percent from already discounted prices pledged to African governments” in 2000 (**Annexure MSD9**). If this is correct, EFV had previously been sold for somewhere between US\$830 and US\$1,000 for a year’s supply for one adult.

42. Since then, Merck has announced the following price reductions of EFV:

- a) 23 October 2002: US\$346.75 (600mg)
- b) 7 March 2006: US\$394.20 (200mg) and US\$277.40 (600mg)
- c) 14 February 2007: US\$237.25 (600mg).

These prices are set out in **Annexure MSD10**, **Annexure MSD11** and **Annexure MSD12** respectively.

43. Reputable generic companies have ordinarily been able to undercut Merck’s prices. Most of the following price data has been sourced from various editions of the Médecins Sans Frontières (“MSF”) document entitled *Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries* (“Untangling the web”). Only the relevant pages of the various editions have been attached. The various editions of the document, which are available online at <http://www.accessmed-msf.org/prod/view.asp?catid=1&>, will be made available upon request.

- a. In September 2001, when Merck’s price was US\$500, the best generic price was US\$ 485 (**Annexure MSD13**).
- b. In December 2002, when Merck’s price for 200mg EFV was still US\$500, the best generic price had dropped to US\$438 (**Annexure MSD14**). At that time, Merck was offering the lowest price for 600mg EFV.

- c. By July 2006, when Merck's prices for EFV were at US\$394.20 (200mg) and US\$277.40 (600mg) respectively, the best generic prices had dropped to US\$225 and US\$217 respectively (**Annexure MSD15**).
 - d. Merck's February 2007 price reduction of 600mg EFV to US\$237.25 was subsequently bettered by generic companies, which have agreed to supply the Clinton Foundation HIV/AIDS Initiative ("CHAI") Procurement Consortium with 600mg EFV at US\$164 – a saving of almost 31% when measured against Merck's current best price. The relevant CHAI document is attached marked **Annexure MSD16**.
 - e. The lowest price for generic 200mg EFV now stands at US\$185 – less than half the current price of Merck's equivalent product (**Annexure MSD17**).
44. Generic companies are also able to undercut Merck's US\$613.20 price for the combination TDF/FTC/EFV (**Annexure MSD16**):
- a) In terms of a recent agreement with the CHAI Procurement Consortium, Matrix Laboratories has agreed to supply a generic version of the combination for US\$385 per adult per year – a saving of over 37% when measured against Merck's price.
 - b) Matrix also produces a similar combination that replaces FTC with 3TC. According to Wood, FTC and 3TC are the only two ARV medicines that can indeed be considered as substitutable for each other. The combination TDF/3TC/EFV is available to the CHAI Procurement Consortium for US\$339 per adult per year. This represents a saving of almost 45% when measured against Merck's price for TDF/FTC/EFV.
45. Generic companies have been able to reduce their prices without having access to significant economies of scale. Because of the price differential between EFV (US\$164 for the best CHAI price) and NVP (\$US45 for the best CHAI price), the NNRTI of choice in most of the developing world is NVP. Brazil – which runs the largest public sector ARV treatment programme outside of South Africa – has until very recently provided

access to EFV only in the form of Merck's patented product. South Africa and Botswana continue to do so.

46. In South Africa, more than two-thirds of all public sector patients accessing ARV treatment are understood to be using EFV. This amounts to more than 230,000 people currently using EFV as part of their ARV treatment in the public sector. Applying a similar breakdown to the private sector yields an estimate of over 70,000 people on ARV treatment who are currently taking EFV. These estimates of numbers of people on ARV treatment in South Africa are based on the work of the Joint Civil Society Monitoring Forum ("JCSMF"), described in Fatima Hassan's affidavit which is attached marked **Annexure FH**.
47. Implicit in Johnson's expert affidavit is that we can estimate between 700,000 and 930,000 people to be using EFV as part of ARV treatment in the public sector by the end of 2011. If generic companies had access to this already substantial and increasingly expanding market, the marginal costs of production could drop significantly. With sufficient competition, this would likely result in further price reductions.
48. Aspen, the first of MSD's two licensees in respect of stand-alone EFV products, does not appear to be one of the generic companies that are able and willing to undercut Merck's best prices. To date, the best price to which it has committed itself in the event that it ever brings EFV products to market is US\$240 for the 600mg tablet. It has made no commitments whatsoever in respect of other EFV products (**Annexure MSD18**).
49. Adcock, MSD's second licensee, has not been able to commit to any particular price. Instead, its managing director has been reported as saying that Adcock will bring EFV to market "at a significant discount to MSD's version" (**Annexure MSD19**, available online at http://www.adcock.co.za/Media_News.aspx?Year=2007&Month=7). Importantly, he "was unable to provide an exact figure, saying it would depend to some extent on the volumes sold." The complainant is of the view that this constitutes more a wish than any realistic or definite commitment.

50. If and when the two licensees bring their 600mg EFV tablets to the South African market, they will only have to price their products marginally lower than MSD's US\$237.25 price to capture significant shares of the private market. In the absence of other licensees, they would not be under competitive pressure to lower their prices further. In respect of the public sector tender, they may even be able to charge more than MSD in the likely event that local manufacturers are afforded some margin in order to further government's stated industrial policy agenda. Only further licensees will be able to ensure that the two licensees, both of whom produce locally, are compelled to compete on the basis of price.

The need for cheaper ARV prices

The NSP on price reductions

51. The NSP identifies the need for steps to be taken to reduce the cost of ARV medicines so as to ensure that it is indeed feasible to implement the plan. The low-cost scenario (which sees only 60% of new AIDS cases accessing treatment by 2011) identifies ARV treatment as responsible for 46% – adults (40%) and children (6%) – of the total cost of the NSP (table 3 at page 117 of the NSP). The high-cost scenario (which sees 80% of new AIDS cases accessing treatment by 2011, in line with one of the two primary goals of the NSP) identifies ARV treatment as responsible for 51% – adults (44%) and children (7%) – of the total cost of the NSP (table 4 at page 118 of the NSP).
52. In respect of price reductions, the NSP states as follows (at pages 116 and 121 respectively):

The cost implications of the NSP are large, in some options exceeding 20% of the health budget without considering the costs arising from the effect of the epidemic on hospital and primary care services. In attempting to increase the feasibility of this plan ... [a]ttention should be placed on increasing the affordability of medicines.

...

It is estimated that, at current prices, the provision of antiretroviral therapy will account for about 40% of the total cost of the NSP. This much needed service will soon be unaffordable at the current drug prices.

53. The message in the NSP is clear: its ambitious targets can not be reached at the current ARV medicine prices. An analysis of the first (and to date only) national ARV medicine tender (**Annexure MSD20**) shows that the most appropriate and feasible way to ensure that overall ARV medicine costs are reduced is by ensuring that the public sector is able to procure cheaper EFV and/or LPV/r products. These medicines collectively accounted for \pm 63.9% of the value of the tender, even though only \pm 24.3% when measured in terms of volume. Collectively, the balance of \pm 36.1% (in terms of value) – accounting for \pm 75.7% in terms of volume – was made up by seven other ARV medicines. Unfortunately, generic companies internationally have not yet been able to undercut the best international price charged for patented LPV/r, meaning that EFV remains the only ARV medicine on the current tender list in respect of which significant price reductions are at present possible.
54. Implicit in the NSP is that medically necessary and public health appropriate revisions to public sector ARV treatment protocols may not be feasible if they would bring with them significant cost implications. Put simply, cost may be the only factor preventing more appropriate first-line regimens (such as TDF + FTC (or 3TC) + EFV) from being introduced. At medicine costs of US\$613.20 per adult per year (MSD's TDF/FTC/EFV product), the public sector may find it impossible to provide universal access to ARV treatment. But at US\$339 (Matrix Laboratories' TDF/3TC/EFV), which is lower than the current price paid by the public sector for regimen 1a (d4T + 3TC + EFV), a change is indeed possible.

Limited access in the Western Cape

55. While there are numerous factors that currently limit access to ARV treatment in the South African public sector, the complainant has been advised that but for the high cost of EFV, many more patients in the Western Cape – which has residual capacity to provide ARV treatment – would be able to benefit from this potentially life-saving medical

intervention. If the respondents were to license multiple generic companies to import and/or manufacture EFV products, the public sector in the Western Cape would be able to treat many more patients than it can currently do. Without access to cheaper ARV medicines, the Western Cape Department of Health is unable to save the lives of many patients with HIV/AIDS who are in need of treatment and cannot afford to access it in the private sector.

56. Unfortunately, the complainant has been unable to access the official Western Cape document in which this allegation is confirmed. It has been obliged to rely upon private communications from concerned individuals working within or advising the provincial government. The complainant therefore requests the Commission to approach the Western Cape Department of Health for assistance in obtaining the relevant document. If the Commission is unable to obtain it, the complainant would be willing to advise it regarding whom in particular to contact.

Exclusion of co-formulated and/or co-packaged ARV products from the market

57. In his expert affidavit, Wood explains that the higher the pill burden – the number of tablets, capsules or other dosage forms that a patient takes on a regular basis – the less likely a person is to adhere to ARV treatment. Conversely, increased adherence is associated with lower pill burdens. Wood further explains the necessity for high levels of adherence to ARV treatment, and the negative impact of low levels of adherence on individual treatment outcomes.
58. There are numerous ways in which the pill burden may be reduced. These include:
 - a) reducing the frequency of taking pills by –
 - i. using products with long-acting active pharmaceutical ingredients (“APIs”); or
 - ii. developing sustained or extended release versions;
 - b) combining standard strengths of more than one API in a single pill, known as a fixed-dose combination (“FDC”); or

- c) co-packaging two or more separate pills in a single blister pack.
59. As already mentioned, two FDCs that contain EFV – TDF/FTC/EFV (to be marketed in South Africa as Atripla™) and TDF/3TC/EFV – have already been developed. There appears to be no scientific reason why EFV could not be combined in a single pill with other ARV medicines that are also taken once daily and ordinarily form part of treatment regimens containing EFV. If this were done, FDCs such as FTC/EFV, 3TC/EFV, ddi/FTC/EFV and ddi/3TC/EFV could theoretically reach the market. But as indicated above, the respondents' refusal to license any generic company to import and/or manufacture FDCs containing EFV and at least one other ARV medicine is an absolute bar to products such as TDF/3TC/EFV reaching the South African market.
60. Some multinational generic companies – including those that have subsidiaries in South Africa – market the following co-packaged products containing EFV in other countries:
- a) AZT/3TC + EFV;
 - b) d4T/3TC + EFV; and
 - c) 3TC + ddi + EFV.
61. Once again, the respondents' refusal to license on reasonable and non-discriminatory terms constitutes an absolute bar to such products reaching the South African market.

Threats to the sustainability of supply

62. The *Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa* ("the Operational Plan"), adopted by Cabinet on 19 November 2003 (more recently incorporated into the NSP) and in terms of which ARV treatment is provided in the public sector, recognises that a "central component of HIV and AIDS care and treatment is the production, procurement and supply of medicines, in particular antiretrovirals" (at page 143). The executive summary of the Operational Plan is attached marked **Annexure MSD21**. The full plan is available online at <http://www.info.gov.za/issues/hiv/careplan.htm> and will be made available upon request.

63. The Operational Plan recognises that in order to support its proper implementation, the drug procurement system must – amongst other things – ensure that the supply of medicines is “secure and sustainable at a volume large enough to meet the significant demand envisioned” (at page 143). In particular, it recognises – at pages 145 and 146 – that a multiplicity of suppliers is necessary to ensure sustainability of supply:

A number of viable and competing manufacturers will also guarantee security of supply should any supplier fail for any reason. ... There is always the risk of failure in the supply chain of pharmaceuticals. It is intended that the procurement plan coordinates a sustainable supply through the participation of viable suppliers, and local production of finished products and active pharmaceutical ingredients.

64. In his expert affidavit, Wood explains what would happen to a person using EFV as part of ARV treatment if the medicine in question were – for whatever reason – to become unavailable. In his focus on ARV treatment that is ordinarily accessed in the public sector, Wood comes to the following conclusions (at paragraphs 59 and 60):

For these reasons, in my considered expert opinion, if EFV were not available to health care workers for the treatment of patients, it would have serious public health consequences. ...

I should also point out that unintended consequences of interrupted treatment, irrespective of the regimen are:

- a) An undermining of adherence messages and patient confidence in the health care system (why should patients be adherent when the health system is unable to provide a sustainable supply of medicines?); and
 - b) An increased risk of AIDS and death, especially in those patients who had very low CD4 counts at treatment initiation, where treatment interruption is for a significant duration of time.
65. Johnson’s expert affidavit places Wood’s conclusions in context. He estimates that between 1.25 and 1.54 million people will be on ARV treatment in the public sector by the end of 2011, of which 204,000 and 149,000 respectively will be on second-line treatment. In other words, between 1.046 and 1.391 million people will be on a first-line

regimen at that time. If the current pattern remains, with more than two-thirds of patients in the public sector accessing EFV instead of NVP, we can estimate between 700,000 and 930,000 public sector patients using EFV.

Evidence of ex-manufacturer shortages

66. There are significant individual clinical and broader public health implications if any ARV medicine used in the public sector is not available (whether in branded or generic form). There is a need for proactive steps to be taken to guard against any potential supply problems in the future. In considering the need for such action, it is important to appreciate that supply problems have already been experienced – in South Africa, in the region, and internationally.

Shortages of EFV

67. Despite the respondents' claims that sustainability of EFV supply is not a cause for concern, there have been a number of occasions when there have been ex-manufacturer shortages of the essential ARV medicine in the region. The complainant is aware of shortages in at least two SADC countries: South Africa and Botswana.
68. In South Africa, shortages have been observed on at least three occasions in the public sector. These shortages are discussed in Berger's affidavit. Additional information regarding EFV shortages is contained in Fatima Hassan's affidavit. As is indicated in Hassan's affidavit, however, it may be necessary for the Commission – by using its statutory powers of investigation – to obtain detailed information from the medical schemes and disease management programmes (DMPs) identified regarding the allegations of EFV shortages. For reasons not known to the complainant, the schemes and DMPs appear hesitant to provide it with detailed information.
69. While the complainant is aware that there have been shortages of EFV in Botswana's public sector caused by Merck's inability to supply product, it is unable to put such evidence before the Commission. It will be able to provide the Commission with the

names and contact details of persons in Botswana who are well placed to provide such evidence and to explain the impact of these EFV stockouts on the Botswana public sector ARV treatment programme.

Shortages of other ARV medicines

70. The complainant has not attempted to conduct an exhaustive search of all ARV medicine shortages that have been experienced in South Africa, the region or internationally. Instead, it has focused largely on documented shortages in respect of the ARV medicines that are the subject of this complaint. However, it is important to note that the threat of a supply shortage is ever present. For this reason, two shortages of other ARV medicines – both of which occurred in Botswana in late 2005 – are considered below.
71. In a letter to the Deputy Permanent secretary in the Ministry of Health in Botswana (dated 8 September 2005 and attached marked **Annexure MSD22**), Conrad Louw – General Manager for GSK Southern Africa – described the reason behind his company's inability to deliver ARV medicines containing AZT timeously:
- [D]ue to the augmented availability of funding from the International donor community over the past couple of months, the global demand for ARV treatment has increased substantially and unexpectedly, putting immense pressure on GlaxoSmithKline's ability to meet new orders within the existing supply dates. As a result of this unforecasted rise in demand, GSK has been forced to extend the lead times for all new orders of ARVs containing zidovudine from the current official level of 16 to 20 weeks.
72. Fortunately, the Government of Botswana was able to source alternative products containing AZT from Aspen in South Africa. In settling the *Tau* complaint in 2002, GSK had agreed to amend an existing licence it had already granted to Aspen so as to permit exports of generic AZT and 3TC products to all sub-Saharan African countries (including Botswana). Prior to the *Tau* case, Aspen's licence from GSK only permitted it to sell to the South African government.

73. At about the same time and as a result of an alleged “moderate shortage in the availability of bulk stavudine globally” in or around October 2005, Bristol Myers-Squibb (“BMS”) informed “customers” – including the Government of Botswana – that it “expect[ed] to have limited stock [of d4T] available until mid 2006”. Disturbingly, BMS suggested that new patients not be initiated on ARV treatment until the shortage had been resolved. The relevant letter from BMS is attached marked **Annexure MSD23**.
74. GSK’s shortage of AZT products could be addressed because other suppliers had indeed been licensed. The only way the d4T shortage could be addressed was by limiting the numbers of patients accessing ARV treatment. Whilst additional licensees would not have mattered in this case (given that the shortage was allegedly as a result of the global shortage of bulk d4T), it does point to the need for additional licensees so as to ensure access to alternative suppliers in the event of shortages as a result of a particular manufacturer’s inability to supply.

Evidence of other supply problems

75. Thus far, this statement of complaint has described product shortages. A greater concern is when a particular product is pulled from the market altogether. This may happen when a product is recalled or when production ceases as a result of manufacturing difficulties. In either case, the availability of generic alternatives is the most appropriate means of averting harm to patients.

Product recalls

76. In a press release dated 14 June 2007 and entitled “WHO STATEMENT ON ROCHE’S VIRACEPT® RECALL”, the World Health Organization (WHO) stated as follows:

“ROCHE informed WHO on 8 June 2007 of its global recall of its nelfinavir products (Viracept®) The reason for the recall is identification of an impurity in some batches of Viracept® The contaminant is a known genotoxic substance.”

According to Wikipedia, a genotoxic substance is a type of carcinogen, in particular one that is “capable of causing genetic mutation and of contributing to the development of tumors”. The WHO statement is attached marked **Annexure MSD24**.

77. In its statement, the WHO advised as follows:

Countries that have included Viracept® in post-exposure prophylaxis packs, should remove and replace it with a suitable boosted protease inhibitor. If no boosted PI are available, dual nucleoside therapy without a PI will remain effective.

Adults or children currently taking Viracept® should not interrupt their antiretroviral therapy. However, they should see their antiretroviral therapy provider as soon as possible, to change from Viracept® to a suitable alternative.

78. Due to the non-availability of generic NFV, patients using Viracept® had no option but to change their treatment regimens. According to a report entitled “Near-global nelfinavir (*Viracept*) recall ‘very difficult situation’” (attached marked **Annexure MSD25** and available online at <http://www.aidsmap.org.uk/en/news/EFA4601B-2827-4131-B2E8-6EB722BEE1D9.asp>), the recall had the following impact in four developing countries:

According to the Latin American News Agency Prensa Latina, Brazil’s Health Ministry – which supplies nelfinavir at no cost to 9,000 adults and 250 children – told clinics to immediately replace *Viracept* with *Kaletra*.

In Botswana, the Ministry of Health is to negotiate with Roche for a refund according to Dr Loeto Mazhani, Director of Health Services in an interview with the Botswana Press Agency. He said that although more than 85,000 individuals are on first-line antiretroviral therapy, fewer than 1,000 patients were taking nelfinavir. He added that patients treated in government or government assisted facilities have also been switched to *Kaletra*.

In Zambia, where Pelekelo Mwangisha, pharmaceutical evaluator of the Zambian Pharmaceutical Regulatory Authority (PRA) told the Zambian *Daily Mail* that nelfinavir was being taken by 100 patients, and that each patient’s doctor would have to decide which drug to switch to. He also said that the PRA is undertaking spot checks in private health centres to ensure that *Viracept* has been taken off the market.

Virawan Taengkaew, deputy secretary general of the Thai Food and Drug Administration (FDA), told *The Nation* newspaper that the recall would affect very few people in Thailand. In 2006, 22 hospitals had prescribed nelfinavir to 190 individuals, but this year just 144 people were taking the drug. She added that individuals taking nelfinavir could ask for compensation if it is proven that they have been harmed by the contamination.

79. Because of the limited numbers of people using NFV as part of ARV treatment – not more than 45,000 globally, with the vast majority living in the developed world – shifts to other ARV medicines were indeed possible. This would not necessarily be so in the case of a product recall, for example, of EFV from South Africa's public sector. As can be gleaned from Johnson's affidavit, South Africa can expect to see at least 700,000 public sector users on EFV by the end of 2011. The public interest is thus best served by ensuring that all reasonable steps are taken to guard against a product recall that could result in such large patient numbers having to change their treatment regimens.
80. In contrast to the impact of the Viracept® recall, a product recall of Cipla-Medpro's AZT/3TC ("Duovir") in South Africa in August 2004 – following concerns relating to the quality of the bioequivalence studies that formed the basis of the medicine's registration – did not result in the need for patients to change regimens. As a press release issued by the complainant at the time noted:

People taking Duovir should know that there are other alternatives to this drug available in South Africa. In addition to Duovir, three other versions of the AZT/lamivudine combination have been registered by the MCC In addition, the MCC has also registered four versions of each of the individual antiretroviral drugs AZT and lamivudine

Attached marked **Annexure MSD26**, the press release is available online at http://www.tac.org.za/newsletter/2004/ns11_08_2004.htm.

Manufacturing problems

81. In July 1998, US-based pharmaceutical company Abbott Laboratories ("Abbott") experienced "manufacturing difficulties" with soft-gel capsule ("SGC") RTV. In a letter to

health care providers in the United States, which is available online at <http://www.fda.gov/medwatch/safety/1998/norvir.htm> and is attached marked **Annexure MSD27**, Abbott explained:

Abbott Laboratories is experiencing manufacturing difficulties with the capsule formulation of our HIV protease inhibitor, Norvir (ritonavir), which will result in a shortage of capsules. We have encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves. It is our plan to supply Norvir oral solution (liquid) to provide continued Norvir therapy for patients. Norvir capsules currently in distribution are not affected by this issue. When used in accordance with the prescribing information, product on the market is safe and effective.

82. Abbott's original optimism regarding shortages appears to have been shortlived. As is noted in "Ritonavir Users Put on Liquid Diet" (*GMHC Treatment Issues*, (July/August 1998) available online at <http://www.thebody.com/content/art13463.html> and attached marked **Annexure MSD28**),"production problems had forced the company to discontinue manufacture of the capsule formulation":

Although the production problem first occurred in June, Abbott waited until the end of July to inform the community, probably hoping to resolve the situation in time to avoid a shortage. Unfortunately, by the time Abbott made its announcement, there was less than a month's worth of capsules left. In order to prevent a run on the supply and stretch out the remaining stock, Abbott controlled inventory by shipping wholesalers only their usual size orders. No additional quantities were sent out nor special orders filled.

On the retail level, pharmacies scrambled to manage supply and demand. At least one major drug store in New York City reported limited quantities of both capsules and liquid by the first week of August and was rationing out seven-day allotments of the drug. Abbott is increasing production of the oral formulation so that by the time pharmacies completely run out of the capsules, there should be enough liquid to meet the demand.

83. SGC RTV did eventually return to the market, some months later. Despite its bad taste, RTV liquid could be used as an alternative in the interim. But if the liquid had not been available, many patients' ARV treatment may have been disrupted completely. At that

stage, LPV/r had not yet reached the market. All other PIs – with the sole exception of NFV – had to be taken with a boosting dose of RTV.

CONCLUSION

84. The TAC and ALP have engaged in a sustained campaign for many years to ensure that MSD and Merck grant multiple non-exclusive voluntary licenses on reasonable and non-discriminatory terms. In response, the respondents have granted two licences on unreasonable grounds. Their failure to act appropriately is to be regretted, but can be addressed, even at this late stage, to avert any future damage.
 85. Should the Commission need any further information, it should not hesitate to contact any of the individual deponents or the ALP, which has filed this complaint on behalf of the complainant. In addition, the ALP will accept service of all documents on behalf of the complainant. The ALP's offices are located on the sixth floor of the Braamfontein Centre, 23 Jorissen Street, Braamfontein, Johannesburg. It can be contacted at (011) 356-4100 (t) and (011) 339-4311 (f).
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