

Under Pressure: Access To Blood Pressure Medicines In Low- And Middle-income Countries

Global sources and prices of anti-hypertensive medicines with a focus on single-pill combinations





Overview

- **Collaboration of RTSL and MSF Access Campaign with the support of two external consultants**
- **March – September 2021: data collection & report writing**
- **14th October 2021: main survey outcomes shared with key partners (e.g., CHAI, Medical University of South Carolina, PAHO, RTI International, WHO)**



Objectives

- Identify gaps and barriers in access to selected HTN medicines that may result in lack of/substandard treatment for patients in LMICs to inform countries and HTN stakeholders to allow a swift implementation of the new WHO 2021 guidelines
- Increase transparency on pricing, registration and availability of WHO-recommended HTN medicines for adults



Methodology

- **Collection of pricing data for selected HTN medicines and formulations**
- **Assessment of the regulatory status of these medicines in a selection of countries**

Country deep dives to explore additional topics that might be relevant for MSF/RTSL operations and advocacy activities

Brazil, Lebanon, Nigeria, The Philippines, South Africa

CRITERIA

- MSF and/or RTSL have operational activities
- MSF and/or RTSL have strong advocacy interest
- Countries with a high burden of HTN
- Representation of different contexts and settings



Methodology: Selection of HTN Medicines

- Presence in the 2019/2021 WHO Essential Medicine Lists (EML) or equivalent to a drug listed in the WHO EML with the square box symbol
- Inclusion of at least one medicine referred to in the steps of the HEARTS algorithms that is either ACEi, ARB, CCB, or thiazide or thiazide-like diuretic, which are also recommended in the WHO 2021 treatment guidelines in adults
- Local availability in specific contexts relevant for the scope of this report

Methodology: Selection of HTN Medicines

Single Agent Pills (SAP)

amlodipine SAP tablet	5mg; 10mg
hydrochlorothiazide SAP tablet	12.5mg; 25mg
lisinopril SAP tablet	20mg; 40mg
losartan SAP tablet	25mg; 50mg; 100mg
telmisartan SAP tablet	40mg; 80mg
valsartan SAP tablet	40mg; 80mg; 160mg; 320mg

Single-Pill Combination (2SPC)

lisinopril + amlodipine SPC tablet	10mg + 5mg; 20mg + 5mg; 20mg + 10mg
lisinopril + hydrochlorothiazide SPC tablet	10mg + 12.5mg; 20mg + 12.5mg; 20mg + 25mg
losartan + amlodipine SPC tablet	50mg + 5mg; 100mg + 10mg; 100mg + 5mg
telmisartan + amlodipine SPC tablet	40mg + 5mg; 80mg + 5mg; 80mg + 10mg
losartan + hydrochlorothiazide SPC tablet	50mg + 12.5mg; 100mg + 12.5mg; 100mg + 25mg
telmisartan + hydrochlorothiazide SPC tablet	40mg + 12.5mg; 80mg + 12.5mg; 80mg + 25mg
valsartan + amlodipine SPC tablet	80mg + 5mg; 160mg + 5mg; 160mg + 10mg

Single-Pill Combination (3SPC)

losartan + amlodipine + hydrochlorothiazide SPC tablet	50 mg + 5mg + 12.5mg
telmisartan + amlodipine + hydrochlorothiazide SPC tablet	40mg + 5mg + 12.5mg; 80mg + 5mg + 12.5mg
valsartan + amlodipine + hydrochlorothiazide SPC tablet	160mg + 5mg + 12.5mg; 160mg + 5mg + 25mg; 160mg + 10mg + 12.5mg; 160mg + 10mg + 25mg; 320mg + 10mg + 25mg



Methodology: Selection of HTN Medicine Manufacturers

- Manufacturers with global registration and supply capacities for HTN medicines
- Mix of generic and innovator companies

1 Accord Healthcare, UK - Intas Pharmaceuticals, India

2 Actavis, US

3 Adcock Ingram, South Africa

4 Apotex, Canada

5 AstraZeneca, UK

6 Aspen Pharmacare, South Africa

7 Aurobindo, India

8 Cadila, India

9 Cipla, India

10 Glenmark Pharma, UK/India

11 GSK, UK

12 Hetero, India

13 Ipca, India

14 Lupin, India

15 Macleods, India

16 Microlabs, India

17 Novartis - Sandoz, Switzerland

18 Strides Arcolab, India / Universal, Kenya

19 Ranbaxy, India - Sunpharma, France/India

20 Teva, US/Israel - Mepha Schweiz AG/Switzerland

21 Viatris, US/India



Methodology: Sources of Data

Regulatory information:

- National databases managed by National Regulatory Authorities (NRAs) with current medicines with a local marketing authorization
- Questionnaire sent to manufacturers to assess registration of selected HTN medicines in 18 LMICs (Bangladesh, Brazil, China, Ethiopia, Ghana, India, Iraq, Jordan, Kenya, Lebanon, Mexico, Nigeria, Philippines, South Africa, Rwanda, Thailand, Turkey, Vietnam)

Standard treatment guidelines and national Essential Medicines Lists:

- MoH websites

Prices in deep dive countries:

- Online MoH pricing databases (Brazil, Lebanon, South Africa)
- Field data collection (Nigeria, The Philippines) inspired on the WHO MedMon methodology



Key Finding: While all national EMLs in the five deep dive countries are aligned with the 2021 WHO EML in regard to inclusion of single agent pills (SAPs), most countries' nEMLs and Standard Treatment Protocols do not include SPCs

	Nigeria	Lebanon	Philippines	Brazil	South Africa
Alignment between WHO EML 2021 and nEML for SAPs	Full Consistency	Full Consistency	Full Consistency	Full Consistency	Partial Consistency
At least one SPC included in nEML	Lack of Consistency	Lack of Consistency	Full Consistency	Lack of Consistency	Full Consistency nEML for PHC encourages the use of SPCs, when available
Medicines in national treatment protocol are included in nEML	Partial Consistency In the national treatment protocol, SPC (amlodipine+ losartan) is preferred to free combination. However, no SPC is included in the nEML	N/A No algorithm found and HTN guidelines do not specify preferred medicines	Full Consistency	N/A No updated guidelines or HTN treatment algorithm found	Full Consistency

LEGEND

Full Consistency

Partial Consistency

Lack of Consistency

RECOMMENDATION: Inclusion of key HTN medicines, particularly SPCs, in national EMLs (aligned with latest WHO Model Lists) and Standard Treatment Protocols, is essential to increase access and improve control rates for people living with hypertension.

Key finding: Based on a sample of seven producers with global manufacturing and supply capacities of generic anti-hypertensive medicines, few SPCs were **registered** in a selection of 18 high-burden LMIC countries.

Manufacturers	Number of HTN formulations registered by at least one SRA		Number of HTN formulations registered by at least one SRA <u>and</u> one of the 18 selected LMICs' NRA*	
	SAPs	SPCs	SAPs	SPCs
Aurobindo	14/15 (93%)	16/28 (57%)	7/15 (47%)	7/28 (25%)
Cipla	2/15 (13%)	3/28 (11%)	2/15 (13%)	3/28 (11%)
Glenmark	2/15 (13%)	3/28 (11%)	2/15 (13%)	3/28 (11%)
Hetero	11/15 (73%)	0/28 (0%)	11/15 (73%) <i>6 SAPs under regulatory assessment in 3 LMICs</i>	0/28 (0%)
Lupin	11/15 (73%)	18/28 (64%)	3/15 (20%)	2/28 (1%)
Macleods	7/15 (47%)	10/28 (36%)	0/15 (0%) <i>3 SAPs under regulatory assessment in 3 LMICs</i>	1/28 (1%) <i>10 SPCs under regulatory assessment in 3 LMICs</i>
Teva	15/15 (100%)	16/28 (57%)	0/15 (0%)	0/28 (0%)

* *List of countries:* Bangladesh, Brazil, China, Ethiopia, Ghana, India, Iraq, Jordan, Kenya, Lebanon, Mexico, Nigeria, Philippines, South Africa, Rwanda, Thailand, Turkey, Vietnam

RECOMMENDATION: Registration of SPCs should be prioritized by National Regulatory Agencies in LMICs as well as by manufacturers.

Key finding: In the five surveyed countries, SPCs tend to be less **available** in the private market compared to SAPs, a situation that is even worse in the public sector. The lower availability of SAPs in public health facilities compared to private pharmacies makes it more expensive for patients to seek and afford treatment for their high blood pressure.

	Formulations registered in the country by at least one manufacturer*		Formulations available in the private sector by at least one manufacturer**		Formulations available in the public sector by at least one manufacturer**	
	SAPs	SPCs	SAPs	SPCs	SAPs	SPCs
Brazil	13/15 (87%)	18/28 (64%)	13/15 (87%)	18/28 (64%)	-	-
Lebanon	12/15 (80%)	14/28 (50%)	12/15 (80%)	14/28 (50%)	12/15 (80%)	14/28 (50%)
Nigeria - Abuja			12/15 (80%)	10/28 (34%)	6/15 (40%)	7/28 (25%)
Nigeria - Kano	11/15 (73%)	15/28 (54%)	12/15 (80%)	14/28 (50%)	11/15 (73%)	14/28 (50%)
Nigeria - Ogun			13/15 (87%)	13/28 (46%)	8 /15 (53%)	5/28 (18%)
South Africa	13/15 (87%)	21/28 (75%)	12/15 (80%)	19/28 (68%)	6/15 (40%)	0/28 (0%)

* Based on any manufacturers that have registered selected medicines in the country, irrespective of the manufacturer selection done for the report.

** Based on any manufacturers that have marketed selected in the country, irrespective of the manufacturer selection done for the report

RECOMMENDATION: Ministries of Health (MoH) should increase the availability of SAPs and, particularly of SPCs, in the public sector.



Estimated cost-based generic prices of key antihypertensive medicines (1/3)

- In 2018, researchers from Harvard University collaborated with WHO to define estimated cost-based generic prices, also referred to as target generic prices, for a broad range of essential medicines, including antihypertensive medicines amlodipine 5 mg and hydrochlorothiazide 25 mg. *(Hill A, Barber M, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Global Health. 2018. Jan 29 8;3:e0005 <https://gh.bmj.com/content/3/1/e000571>)*
- Estimated cost-based generic prices are based on an estimation formula developed by reviewing published analyses of cost of production for medicines and assuming manufacture in India, which included costs of formulation, packaging, taxation and a 10% profit margin.
- In 2021, in collaboration with RTSL and MSF, the same researchers used the methodology developed in 2018 to calculate cost-based generic prices for additional antihypertensive medicines included in the scope of the survey

Estimated cost-based generic prices of key antihypertensive medicines (2/3)

Formulation (tablet)	Estimated cost-based generic price (US\$/tablet)
amlodipine 5 mg	0.012
amlodipine 10 mg	0.0128
hydrochlorothiazide 12.5 mg	0.0118
hydrochlorothiazide 25 mg	0.0124
losartan 25 mg	0.0141
losartan 50 mg	0.0169
losartan 100 mg	0.0225
telmisartan 40 mg	0.0184
telmisartan 80 mg	0.0256
losartan + amlodipine 50 mg + 5 mg	0.0176
losartan + amlodipine 100 mg + 5 mg	0.0232
losartan + amlodipine 100 mg + 10 mg	0.024
telmisartan + amlodipine 40 mg + 5 mg	0.0192
telmisartan + amlodipine 80 mg + 5 mg	0.0263
telmisartan + amlodipine 80 mg + 10 mg	0.0271



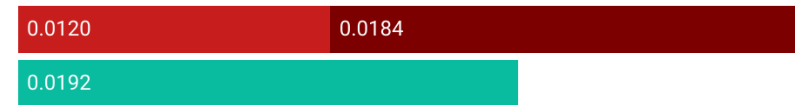
Estimated cost-based generic prices of key antihypertensive medicines (3/3): Comparison of combined SAPs versus SPCs

Price comparison: SAPs vs SPCs

In some settings single-pill combinations (SPCs) are already less costly to use than the sum of the price of their equivalent single agent pills (SAPs). The chart below shows the benchmark or target price (known as the estimated cost-based generic price) of the sum of two single agent pills compared to the single pill combination.

■ amlodipine ■ telmisartan ■ losartan ■ Combination

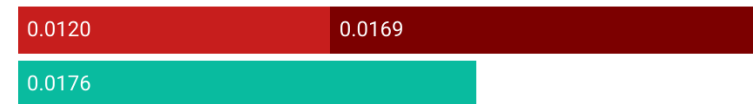
amlodipine 5mg + telmisartan 40mg



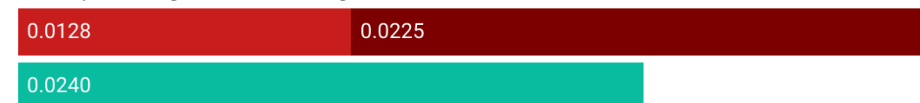
amlodipine 10mg + telmisartan 80mg



amlodipine 5mg + losartan 50mg

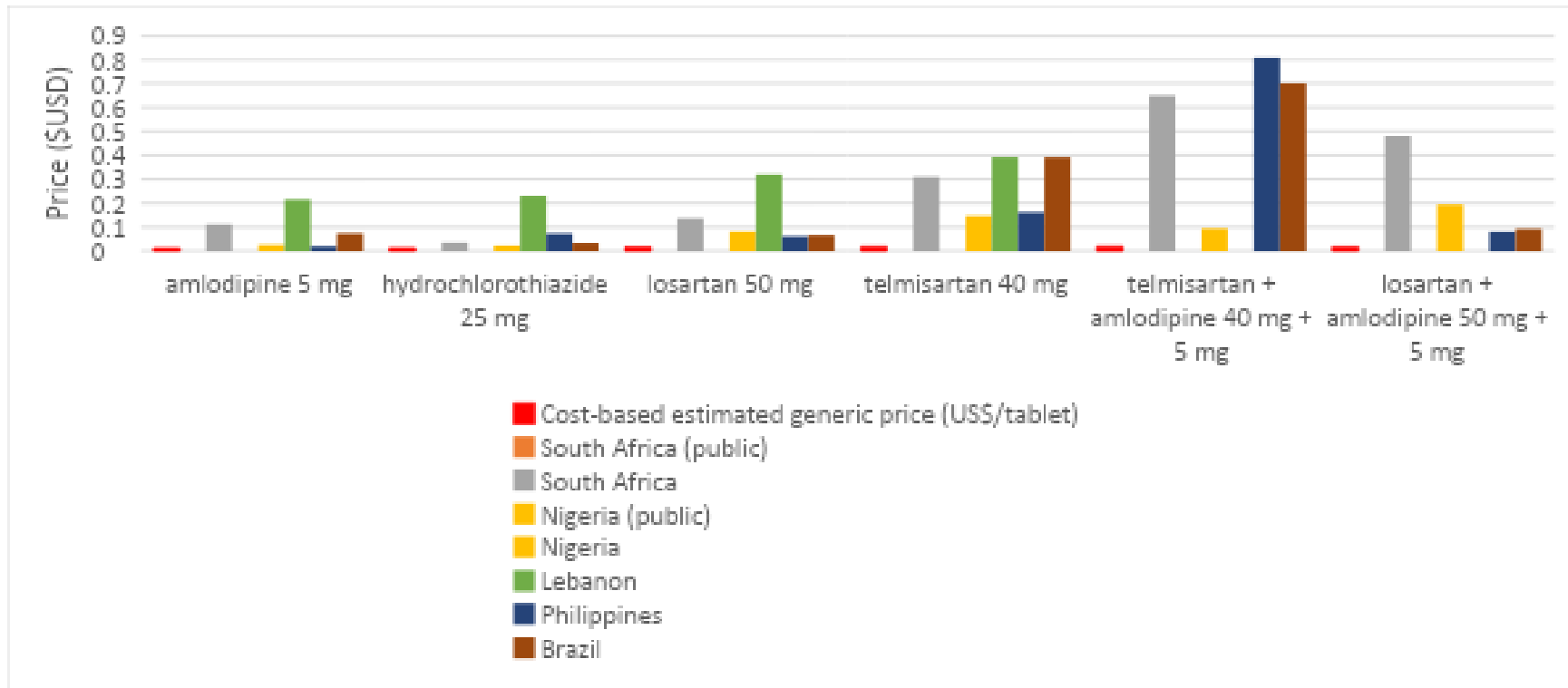


amlodipine 10mg + losartan 100mg



Key finding (1/2): The SAPs and SPCs examined are more expensive than estimated cost-based generic prices in both the private and public sectors of all the countries, except for amlodipine 5 mg and hydrochlorothiazide 25 mg in the public sector in South Africa. Moreover, SPCs are priced much higher than their estimated cost-based generic price compared to SAPs

Private sector



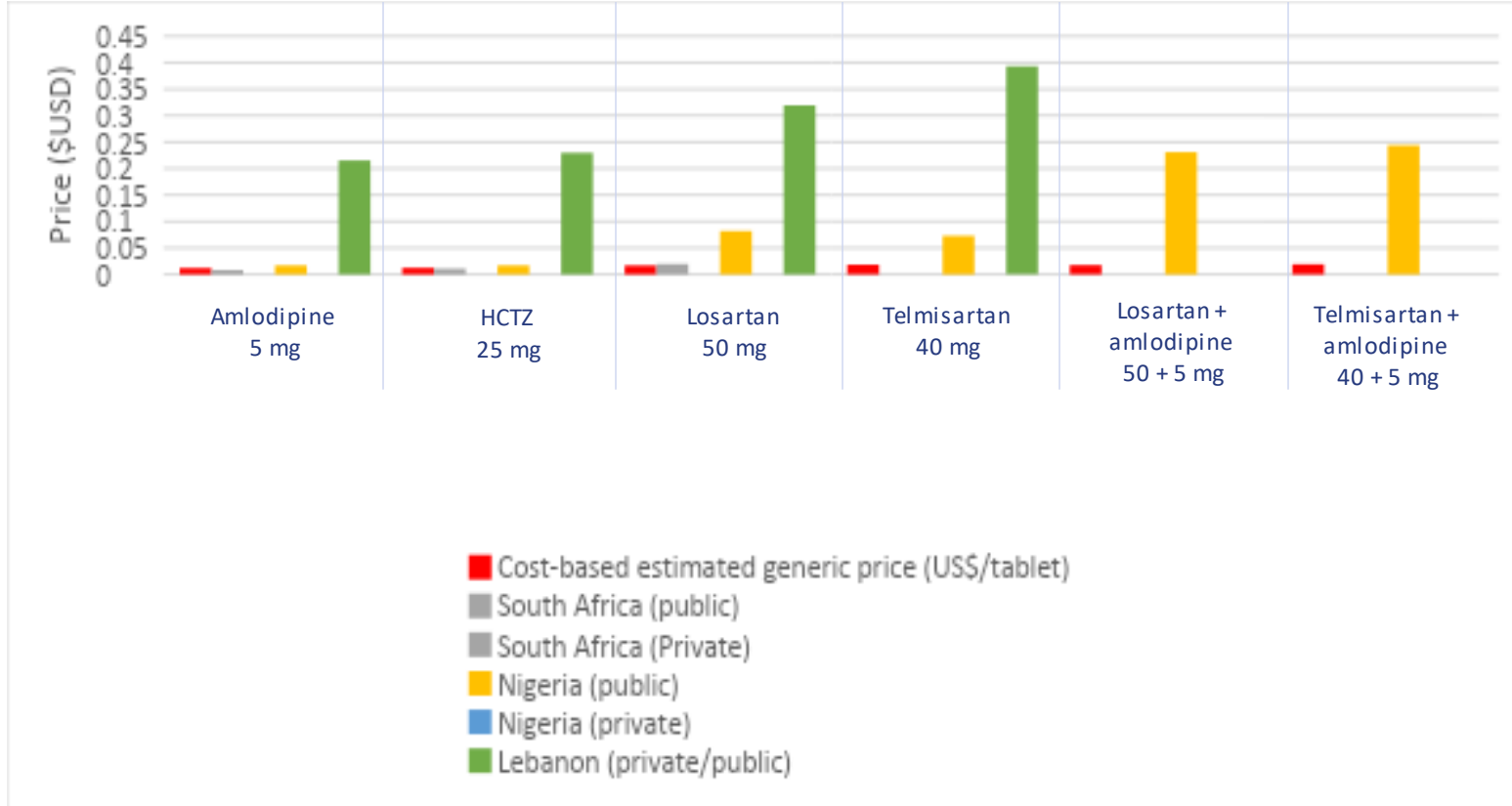
RECOMMENDATIONS:

More efficient procurement strategies should be implemented by countries at government level and by private distributors to procure more affordable HTN medicines. To support purchasers in LMICs in their negotiations with pharmaceutical companies, SPCs and more SAPs should be added to the list of HTN medicines with estimated cost-based generic prices

Countries in other regions could compare HTN prices in their countries with those provided by UNICEF or other pooled procurement mechanisms to identify potential savings.

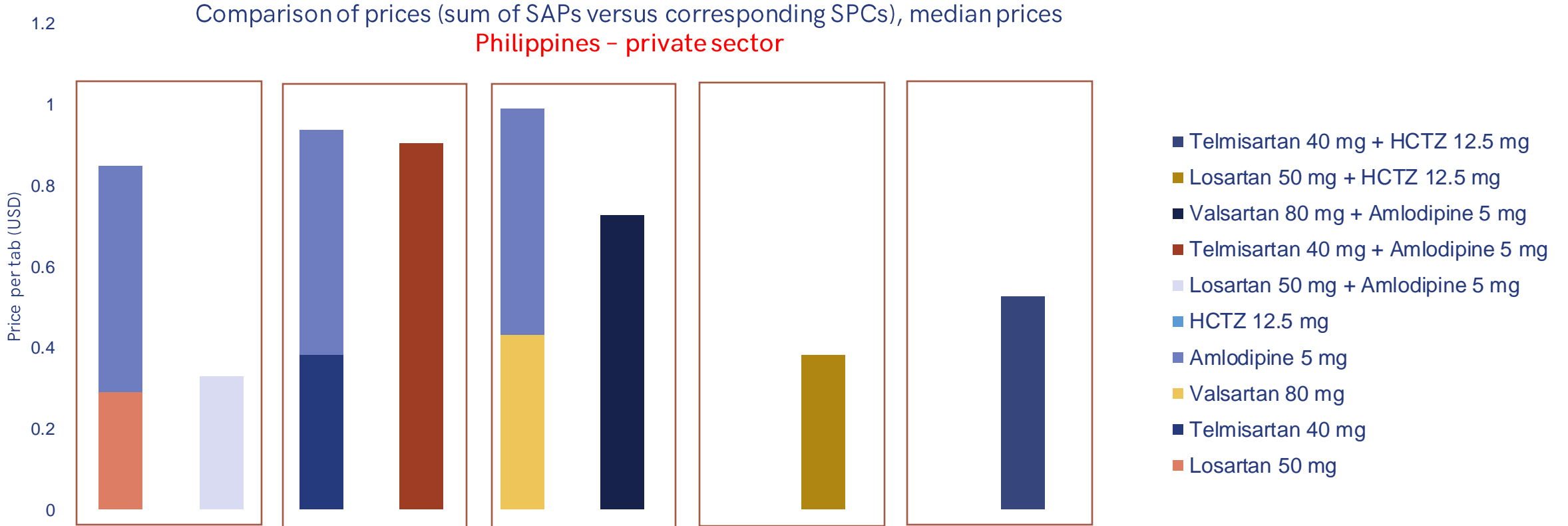
Key finding (2/2): The SAPs and SPCs examined are more expensive than estimated cost-based generic prices in both the private and public sectors of all the countries, except for amlodipine 5 mg and hydrochlorothiazide 25 mg in the public sector in South Africa. Moreover, SPCs are priced much higher than their estimated cost-based generic price compared to SAPs

Public sector





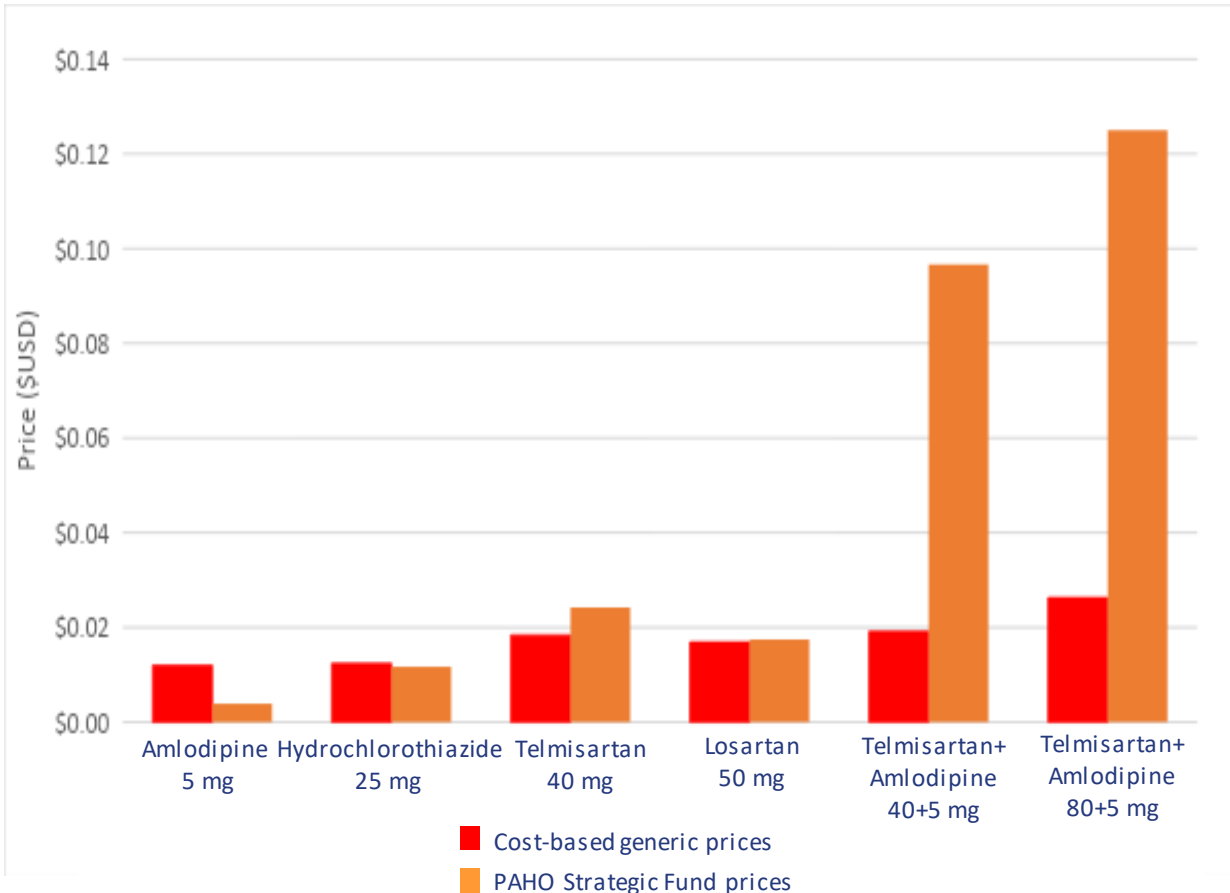
Key finding: While very little data could be collected on SPC pricing in the public sector, out of the limited sample of deep dive countries, SPCs were found overall less expensive compared to the sum of their related SAPs in the private market.



RECOMMENDATION: Countries should not see price as a barrier to implementing SPCs. In fact, use of SPCs may actually be cost-effective from a programmatic point of view. Countries should furthermore look for efficiency gains in their procurement strategies to supply more affordable SPCs.



Key finding: Prices of SAPs that can be procured through the PAHO Strategic Fund are cheaper or comparable to estimated cost-based generic prices for amlodipine 5 mg, HCTZ 25 mg and losartan 50 mg. PAHO Strategic Fund should seek to negotiate more affordable prices for telmisartan 40 mg and the two SPCs.



RECOMMENDATION: LMICs in the Americas should compare their local prices for key SAPs with those provided by the PAHO Strategic Fund to better ensure cost-effectiveness.

Note: incoterms for PAHO drug prices = FOB

Utility of a costing tool developed by RTSL to estimate HTN treatment protocol costs





Costing Tool

- Quantifies financial implications of a treatment protocol based on SAPs and/or SPCs
- Inputs:
 - Total population (source: <http://hdr.undp.org/en/countries>)
 - HTN prevalence (various sources)
 - Percentage of adult population (source: <http://hdr.undp.org/en/countries>)
 - Lowest and highest prices collected in the public and/or private sectors for SAPs and/or SPCs
 - Selection of HTN medicines recommended in the two 2021 WHO algorithms.
- Assumptions for the proportion (%) of persons affected by HTN who are controlled at each step of the corresponding treatment protocol. These assumptions were based on data available from the India hypertension control initiative and were applied across countries.
- Estimates for enrollment and expected monthly loss to follow-up rates
- The yearly budget estimated by the tool was divided by the expected number of enrolled persons. The final figure derived from these calculations is referred to as **"average per-patient treatment cost"** in this report.

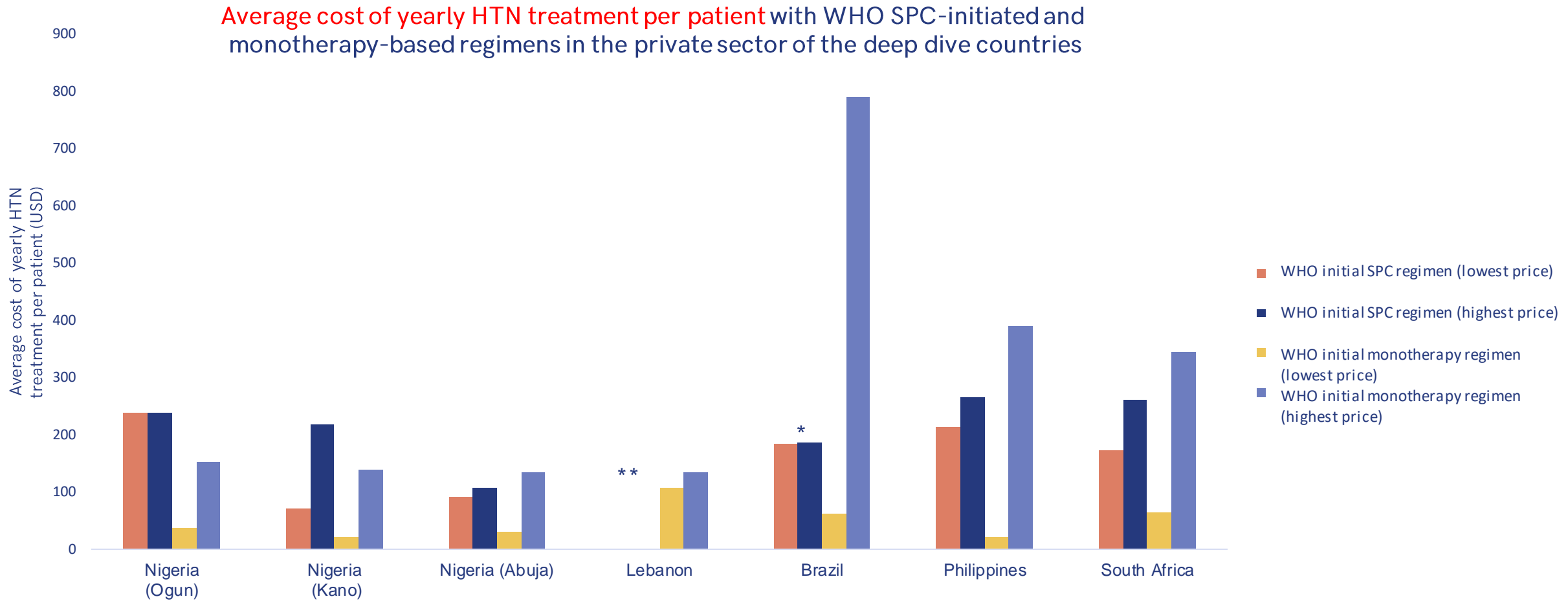
Control assumptions used for each steps of WHO-recommended HTN regimens used in the costing tool

While control assumptions related to SAPs are based on evidence collected in India, those related to SPCs are hypothetical.

Initial SPC regimen	Control assumption
Telmisartan + Amlodipine 40 mg + 5 mg	65%
Increase to: Telmisartan + Amlodipine 80 mg + 10 mg	25%
Telmisartan + Amlodipine 80 mg + 10 mg Add: Hydrochlorothiazide 25 mg	5%
Telmisartan + Amlodipine 80 mg + 10 mg Increase to: Hydrochlorothiazide 50 mg	5%

Initial Monotherapy regimen	Control assumption
Amlodipine 5 mg	40%
Increase to: Amlodipine 10 mg	15%
Amlodipine 10 mg Add: Telmisartan 40 mg	20%
Increase to: Telmisartan 80 mg Amlodipine 10 mg	12%
Telmisartan 80 mg Amlodipine 10 mg Add: Hydrochlorothiazide 25 mg	8%
Telmisartan 80 mg Amlodipine 10 mg Increase to: Hydrochlorothiazide 50 mg	5%

Graph example



Costs of SPC-initiated and monotherapy-based regimens were calculated using the lower strengths of each formulation (e.g., Amlodipine 5mg, Telmisartan 40mg)

* Only one price available for the SPC telmisartan + amlodipine 40mg +5mg in Brazil

** No data available for Lebanon for WHO SPC-initiated regimen due to the lack of telmisartan + amlodipine 40mg + 5mg on the market



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