South African National Essential Medicine List
Primary and Adult Hospital Level of Care Medication Review Process
Component: Cardiovascular conditions – Hypertension in Adults

MEDICINE REVIEW

TITLE: Indapamide as first-line therapy for uncomplicated primary hypertension compared to HCTZ

DATE: 16 July 2021

Key findings

- Hydrochlorothiazide (HCTZ) is currently the first-line pharmacological treatment for hypertension recommended in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa. Indapamide is not currently listed on the EML and is not on national tender. Some clinical guideline recommendations and local clinicians state a preference for thiazide-like diuretics (indapamide, chlorthalidone) over conventional thiazide diuretics (hydrochlorothiazide [HCTZ], chlorothiazide, bendroflumethiazide) for the management of essential hypertension.
- We conducted a review of systematic reviews and clinical practice guidelines that reported on or provided recommendations on first-line use of thiazide diuretics.
- We identified two relevant systematic reviews and three clinical practice guidelines.
- Findings from systematic reviews: There were no direct comparisons between the different diuretics regarding long-term clinical outcomes. Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. This makes it difficult to be certain regarding the comparative efficacy of HCTZ vs indapamide for blood pressure lowering. According to one of the systematic reviews, indapamide reduce left ventricular mass (LVM) 2-fold more than HCTZ in hypertensive patients, but the authors found no difference between the diuretics reviewed and HCTZ for systolic or diastolic blood pressure. Therefore, changes in blood pressure failed to explain the superiority of indapamide in reducing LVM.
- Findings from clinical practice guidelines: The National Institute for Health and Care Excellence (NICE) 2011 guideline recommendation that use of thiazide-like diuretics (e.g. indapamide) are preferred over conventional thiazides (e.g. HCTZ) is based on lack of evidence supporting use of conventional thiazide diuretics, not comparative efficacy. The European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guideline doesn't state preference for either conventional thiazide or thiazide-like diuretics – instead it recommends two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada 2020 guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.
- Estimated pharmaceutical costs (annual cost for estimated patient population likely to start first-line treatment): Indapamide 2.5mg: R28 732 586, Indapamide SR 1.5mg: R203 012 207, HCTZ 25mg: R7 536 416
- The review found that the evidence supporting the use of indapamide over HCTZ is of low quality with uncertain impact on important clinical outcomes. In addition, indapamide is almost four times more expensive than HCTZ and a large patient population will be eligible to receive the treatment each year. Including indapamide as a first-line treatment option will therefore have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/ADULT Hospital Level Committee suggests that indapamide not be recommended for the first-line treatment of patients with uncomplicated hypertension.

Rationale: The clinical evidence supporting the use of indapamide over HCTZ is of low quality and uncertain. In addition, indapamide is more expensive than HCTZ and would have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. Indapamide may be considered for inclusion in the therapeutic interchange database as an alternative to HCTZ.

Level of Evidence: Systematic reviews of lower quality clinical trials and/or inconsistent findings.

Review indicator: Price reduction or new evidence of clinical benefit

NEMLC RECOMMENDATION (24 FEBRUARY 2022):

DISCUSSION

- *Metabolic effects:* It was queried if there would be a place for indapamide amongst diabetics, as approximately 15% of patients on thiazides develop diabetes (evidence not provided). However, the review states that: "Metabolic effects (electrolyte abnormalities, plasma glucose, cholesterol, uric acid levels) were reported in some of the studies included in the NICE 2011 evidence review (see Appendix F), but those outcomes were not reviewed or reported on. A critically low quality systematic review and meta-analysis[a] (with a very similar scope to the NICE 2011 evidence review) assessed the metabolic outcomes reported in the studies included in the NICE 2011 evidence review and reported no significant difference between indapamide and HCTZ on metabolic outcomes.[b]
- *Comparative costing analysis:* The reference for the source of the Indapamide price was omitted, but confirmed to be 100% of SEP. It was recommended that a sensitivity analysis be done for the analysis using 60% of SINGLE EXIT PRICE (SEP).

Recommendations:

- NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence review be circulated for external comment with the PHC cardiovascular chapter.
- A sensitivity analysis of the costing analysis using 60% of SEP be conducted, whilst the draft documents are circulated for external comment.

References:

a. This review was excluded at full-text screening stage due to its low quality and the significant overlap with the NICE 2011 evidence review (which is a higher quality review). See Appendix E for more detail.

b. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects. Hypertension. 2015;65:1041–6. https://pubmed.ncbi.nlm.nih.gov/25733245/

Monitoring and evaluation considerations

No changes to monitoring and evaluation required.

Continue with patient care and follow up guidance provided in STGs (1,2). This includes periodically assessing the level of blood pressure control in primary health care and adult hospital level of care.

Research priorities

1. To determine the level of blood pressure control in South Africa with the currently adopted therapeutic strategies
2. To determine the burden and cost implications of hypertension related complications in the public health sector.
3. To determine the implementation of the stepwise treatment algorithm in clinical practice and what factors contributes to non-implementation

(Refer to the evidence-to-decision framework)

1. EXECUTIVE SUMMARY

Date: 16 July 2021
Medicine (INN): Indapamide
Medicine (ATC): C03BA11
Indication (ICD10 code): I10 – Essential (primary) hypertension
Patient population: Adults aged 18 years or older with uncomplicated primary hypertension
Prevalence of condition: 46% of women and 44% of men aged 15 years and older (SADHS 2016 (3))
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse practitioner, Medical Doctor, Specialist
Current standard of Care: Hydrochlorothiazide (HCTZ)
Efficacy estimates: Blood pressure: Uncertain effect potentially favouring indapamide. Left ventricular hypertrophy: Indapamide is superior to HCTZ by reducing left ventricular mass by -7.5% (-12.7, -2.3).
Budget estimates (annual cost for estimated patient population likely to start first-line treatment):
Indapamide 2.5mg: R28 732 586, Indapamide SR 1.5mg: R203 012 207, HCTZ 25mg: R7 536 416
Motivator/reviewer name(s): Nqoba Tsabedze, Maryke Wilkinson, Trudy Leong, Tamara Kredo

2. NAME OF AUTHORS

Nqoba Tsabedze, Maryke Wilkinson, Trudy Leong, Tamara Kredo

3. AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

- Dr. N Tsabedze: University of the Witwatersrand; Adult Hospital Level Committee, National Department of Health, South Africa; Charlotte Maxeke Johannesburg Academic Hospital.
- Mrs. Maryke Wilkinson: Cochrane South Africa, South African Medical Research Council and Better Health Programme South Africa.
- Ms. Trudy Leong: Essential Drugs Programme, National Department of Health, South Africa.
- Dr. Tamara Kredo: Cochrane South Africa, South African Medical Research Council and Division of Clinical Pharmacology, Department of Medicine, Stellenbosch University.

NT, MW, TL, TK have no conflicts of interest to declare pertaining to Indapamide.

4. ACKNOWLEDGEMENTS

- Mrs. Joy Oliver (Cochrane SA, SA Medical Research Council) for developing and implementing the search strategy.
- Dr. Leah Ferguson (Red Cross Children's Hospital) for assisting with AGREE II assessments.

5. INTRODUCTION/ BACKGROUND

Description of the condition

In South Africa, the probability of premature mortality between the ages of 30 and 70 due to non-communicable diseases (NCDs) is 34% for males and 24% for females (total 29%). Most of these NCD-related deaths are due to cardiovascular disease (CVD), followed by cancer, diabetes and chronic respiratory disease (4). Hypertension is a major risk factor for cardiovascular diseases such as stroke and ischaemic heart disease.

The South Africa Demographic and Health Survey (SADHS) showed that 46% of women and 44% of men aged 15 years and older have essential hypertension. Since 1998, national prevalence of hypertension has nearly doubled[1], from 25% to 46% among women and from 23% to 44% among men (3).

The national incidence of hypertension expressed as the number of newly diagnosed cases per annum per 1000 population aged 40 years and older, was 18.9 in 2016/2017 (5).

[1] Note: different instruments were used to measure blood pressure in the two surveys (Omron M1 in 1998 and Omron 1300 in 2016).

Description of the interventions
An overview of the intervention under review is provided in Table 1.

Table 1. Description of the intervention

Information Field	Details	Reference
Name of the technology	International Nonproprietary Name((INN): Indapamide Proprietary names: Multiple (see Appendix A)	SAHPRA (6)
Licensing status	SAHPRA registered	SAHPRA (6)
Reimbursement status	Not currently approved for use on EML for any level of care, and not on national tender.	Master Health Product List (7)
ATC classification	C03BA11	
Mechanism of action	Indapamide exhibits an antihypertensive action. The antihypertensive effect of indapamide is due to the reduction in the total peripheral and arterial vascular resistance and possibly involves both renal and extra-renal effects.	Indapamide package insert (8)
Indication relevant to this review	Management of mild to moderate hypertension.	Indapamide package insert (8)
Dosage form and strength(s)	Indapamide 2,5mg tablet (30 tablet pack) Indapamide 1,5mg sustained-release tablet (30 tablet pack)	SAHPRA (6)
Route of administration	Oral	SAHPRA (6)
Dosage regimen	Once daily (morning)	Indapamide package insert (8)
Setting	Primary and hospital level	
Additional tests or investigations required to administer technology	No additional requirements in addition to those required when prescribing hydrochlorothiazide	
Anticipated place in therapy	First-line pharmacological treatment for essential hypertension	
Comparator(s)/ Standard of Care	Hydrochlorothiazide – 12,5mg and 25mg (28 tablet packs) (see Appendix B)	

ATC - Anatomical Therapeutic Chemical, EML - Essential Medicines List , SAHPRA - South African Health Products Regulatory Authority

Hydrochlorothiazide (HCTZ) is currently the first-line pharmacological treatment for hypertension recommended in the Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for South Africa - Primary Healthcare Level (2020 Edition) (1) as well as the Adult Hospital Level STG and EML (2). HCTZ has a once-daily dosing regimen, and is available in doses of 12,5mg, 25mg and 50mg per tablet. The 50mg HCTZ tablet is not recommended for use in the STGs. Contraindications for HCTZ are gout, pregnancy, severe liver impairment, and kidney impairment (eGFR < 30 mL/min), and it should be used with caution in patients with a history or family history of skin cancer. All patients on HCTZ must be counselled on sun avoidance and sun protection (1).

Indapamide is not currently listed on the EML and is not on national tender. Indapamide has a once-daily dosing regimen, and is available in doses of 2,5mg (tablet) and 1,5mg (sustained-release tablet). A larger dose than 2.5mg indapamide daily is not recommended. Contraindications for indapamide are renal impairment (eGFR < 30 mL/min), hepatic encephalopathy or severe impairment of liver function, and hypokalaemia. Safety in pregnancy and lactation has not been established.

Why it is important to do this review
Some clinical guideline recommendations state a preference for thiazide-like diuretics (indapamide, chlorthalidone) over conventional thiazide diuretics (HCTZ, chlorothiazide, bendroflumethiazide) for the management of essential hypertension.

“The thiazide-like diuretics retain the main action of thiazide diuretics, i.e. inhibition of the sodium chloride co- transporter in the distal nephrons of the kidney. However, the thiazide and thiazide-like drugs have differential effects on other enzyme effects in the kidney, e.g. carbonic anhydrase inhibition, which can differ by up to 10,000-fold. Differential effects

on platelet aggregation and regulation of angiogenesis have also been reported. The relevance of these actions beyond the characteristic thiazide action of inhibition of the sodium chloride cotransporter with regard to blood pressure control and the prevention of clinical outcomes is unknown." [NICE 2011 evidence review (9)] Furthermore, these potential benefits may only be realised after chronic use and not immediately realised.

This review aims to investigate the relative clinical efficacy of indapamide versus HCTZ, and present how clinical guideline panels interpreted the evidence when they developed recommendations regarding first-line use of thiazide diuretics. The relative costs of indapamide and HCTZ and pharmaceutical budget impact is also presented for consideration in addition to the evidence and discussion of the relative clinical effect.

6. PURPOSE/OBJECTIVE

Review question: Should indapamide be used for first-line therapy for uncomplicated primary hypertension, compared to HCTZ?

Table 2. Scope of the technical review

Population	Adults aged 18 years or older with uncomplicated primary hypertension - No congestive cardiac failure (Loop diuretics preferred) - No resistant hypertension (Patients should be on a diuretic and add-on spironolactone is preferred)
Intervention/s and comparisons	Intervention: Indapamide (immediate- and slow-release formulations) Comparator: Hydrochlorothiazide
Outcomes	**Primary outcomes:** - Blood pressure reduction (in mmHg) - Systolic and diastolic BP (in mmHg) - Major adverse cardiovascular effects: stroke, myocardial infarction **Secondary outcomes:** - Asymptomatic target organ damage - Microalbuminuria - Chronic kidney disease (CKD) - Retinopathy - Left ventricular hypertrophy - Metabolic effects: ▪ Dyslipidaemia ▪ Glucose control (HBA1c changes) ▪ Electrolyte abnormalities: Hypokalaemia, hyponatremia **Clinical Effects:** - Hypotension (postural)
Study designs	Systematic reviews of trials Clinical practice guidelines

7. METHODS

We conducted a review of the evidence including systematic searching on two electronic databases: PubMed and the Cochrane Library. The search strategies for the systematic literature searchers in PubMed and the Cochrane Library are shown in Appendix C. Title and abstract and full-text screening for systematic reviews were done in duplicate using COVIDENCE software. One reviewer summarised the included systematic reviews; a second reviewer checked the results. The AMSTAR (A MeaSurement Tool to Assess systematic Reviews) instrument was used to appraise the methodical quality of the systematic reviews selected for inclusion. AMSTAR assessments were done in duplicate, with disagreements resolved through discussion.

In addition, a search for relevant clinical practice guidelines was completed using the following databases: World Health Organization (WHO), Guidelines International Network (GIN), National Institute for Health Care Excellence (NICE), and the

Scottish Intercollegiate Guidelines Network (SIGN). One reviewer used simple, broad search terms, including 'hypertension' and 'cardiovascular' in the electronic searches for clinical guidelines. One reviewer extracted the relevant recommendations from the clinical guidelines, and this was checked by a second reviewer. AGREE II (Appraisal of Guidelines, for Research, and Evaluation) assessments was carried in duplicate of clinical guidelines selected for inclusion to evaluate the process of guideline development and quality of reporting.

8. FINDINGS

Systematic reviews

Two electronic databases (PubMed and the Cochrane Library) were searched on 29 April 2021 and sixty systematic reviews were identified. Two additional systematic reviews were identified through checking reference lists of eligible reviews and clinical guidelines. After title and abstract screening, six systematic reviews were selected for full-text screening, from which two eligible systematic reviews were selected (9,10) for inclusion, and AMSTAR II assessments were completed for both the reviews (see Appendix D). The four systematic reviews excluded at full text screening (and the reason for their exclusion) are presented in Appendix E. The Prisma flow diagram for the search output is shown below (figure 1).

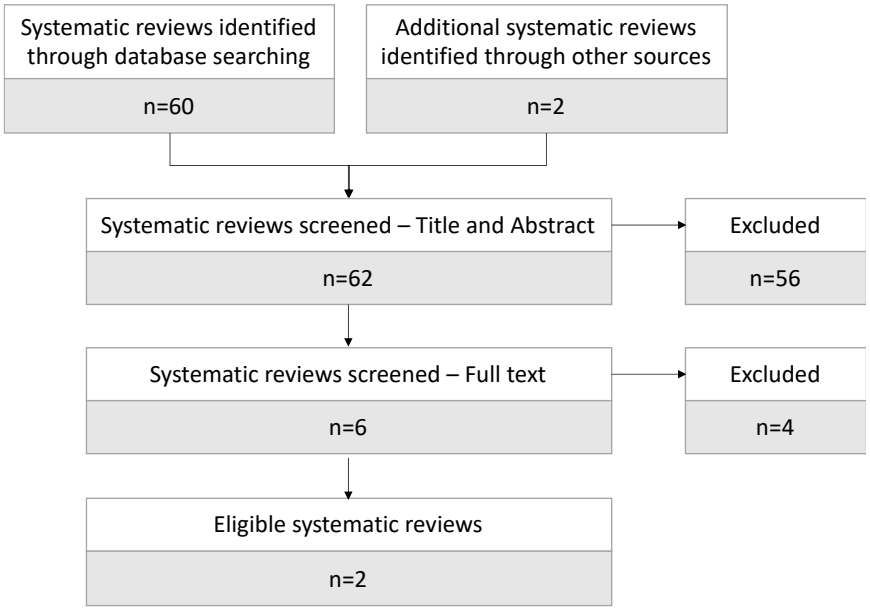


Figure 1. Prisma flow diagram of search results: systemic reviews

The evidence review that most closely corresponded to our review question and had the highest AMSTAR II score was commissioned by NICE (conducted by the Royal College of Physicians, published in August 2011 (9)) to inform *NICE Clinical Guideline 127: The clinical management of primary hypertension in adults.* One of the thirteen review questions selected for systematic review as part of the update of NICE CG 127 was: *In adults with primary hypertension, which is the most clinically and cost-effective thiazide diuretic (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment, and does this vary with age and ethnicity?*(9)

The other systematic review selected for inclusion was conducted by Roush et al in 2018 (10). Roush et al 2018 tested the hypothesis that "CHIP" diuretics (CHlorthalidone, Indapamide, and Potassium-sparing diuretic/hydrochlorothiazide [PSD/HCTZ]) are superior to HCTZ for reducing left ventricular mass (LVM) in hypertensive patients (10).

A summary of the methods and findings from the two included systematic reviews are presented below.

A. <u>NICE 2011 evidence review</u> (9) – ***AMSTAR II assessment: Moderate quality review***

- The analysis examined data for the four most commonly used thiazide-type diuretics:
  i) conventional thiazide diuretics (e.g. bendroflumethiazide and HCTZ), and
  ii) thiazide-like diuretics (e.g. chlorthalidone and indapamide).
- The review included studies that compared hypertensive patients taking one of the four diuretics as first-line therapy with each other. Patients that were exclusively diabetic or had CKD were excluded, and outcomes of interest were BP measurements.
- A total of 15 RCTs were found that fulfilled the inclusion criteria, of which six RCTs compared indapamide with HCTZ (11–16) and one compared indapamide with placebo (17). See characteristics of included studies in Appendix F.
- Head-to-head comparisons were usually based on blood pressure changes as the main outcome.
- There were no direct comparisons between the different diuretics with regard to clinical outcomes.
- HCTZ–indapamide comparison evidence of systolic blood pressure (SBP) and diastolic blood pressure (DBP):
  - Table 3 summarises the quality of the evidence and outcome data for the studies included in the review.
  - The studies were often of short duration (did not allow for hard outcomes evaluation) and the NICE guideline development group considered all of them to be underpowered to detect a significant blood pressure difference between diuretic treatments. A sample size of N > 500 is required in order to detect a 5 mmHg difference in the two arms. Furthermore, there was considerable variation in the doses of diuretics used in the various studies.
  - The results of the meta-analyses are presented in Table 4.
  - "The results of the meta-analyses comparing indapamide and HCTZ for SBP and DBP (supine and upright) should be interpreted with extreme caution due to the observed significant heterogeneity. This appears to be attributed to one of the RCTs (11) which reports an effect size in the opposite direction to the other studies and because it has much smaller standard deviations than the other trials, it has therefore been weighted more highly. If this trial is removed from the meta-analysis then heterogeneity is reduced to more acceptable levels of 0% and the effect becomes not significant. Removing the two lower quality trials (12,13) from the analysis did not result in removing the observed heterogeneity. If a random effects model is applied to the pooled estimate, then the effect size also becomes not significant."(9)
- Metabolic effects (electrolyte abnormalities, plasma glucose, cholesterol, uric acid levels) were reported in some of the studies included in the NICE 2011 evidence review (see Appendix F), but those outcomes were not reviewed or reported on. A critically low quality systematic review and meta-analysis[2] (with a very similar scope to the NICE 2011 evidence review) assessed the metabolic outcomes reported in the studies included in the NICE 2011 evidence review and reported no significant difference between indapamide and HCTZ on metabolic outcomes (18).

[2] This review was excluded at full-text screening stage due to its low quality and the significant overlap with the NICE 2011 evidence review (which is a higher quality review). See Appendix E for more detail.

Table 3: Evidence Thiazide-like diuretics vs Thiazide diuretics (Indapamide versus hydrochlorothiazide) [Table 72 in NICE 2011 evidence review (9)]

Quality assessment						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Indapamide vs HCTZ**	**Control**	**Relative**	**Absolute**	
SBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
5 (11–14,17)	RCTs	Serious[1]	very serious[2]	no serious indirectness	no serious imprecision	77	74	-	MD 8.36 lower (10.92 to 5.8 lower)	VERY LOW
DBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
5 (11–14,17)	RCTs	very serious[1]	Serious[3]	no serious indirectness	no serious imprecision	77	74	-	MD 4.2 lower (5.48 to 2.92 lower)	VERY LOW
SBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
4 (11,12,14,17)	RCTs	no serious limitations	very serious[4]	no serious indirectness	no serious imprecision	54	55	-	MD 8.74 lower (11.75 to 5.73 lower)	LOW
DBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)										
4 (11,12,14,17)	RCTs	no serious limitations	very serious[5]	no serious indirectness	no serious imprecision	54	55	-	MD 3.85 lower (5.41 to 2.28 lower)	LOW
SBP supine (change from baseline) (follow-up 3-6 months; measured with: mmHg; Better indicated by lower values)										
2 (14,16)	RCTs	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	196	192	-	MD 3.95 lower (7.03 to 0.87 lower)	MODERATE
DBP supine (change from baseline) (follow-up mean 3-6 months; measured with: mmHg; Better indicated by lower values)										
2 (14,16)	RCTs	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	196	192	-	MD 0.76 lower (2.5 lower to 0.98 higher)	MODERATE
SBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)										
1 (14)	RCTs	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	18	21	-	MD 12.55 lower (17.11 to 7.99 lower)	HIGH
DBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)										
1 (14)	RCTs	no serious limitations	no serious inconsistency	no serious indirectness	Serious[7]	18	21	-	MD 2.07 lower (7.2 lower to 3.06 higher)	MODERATE
SBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 5.5 higher (0 to 0 higher)[9]	MODERATE
DBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 5.9 higher (0 to 0 higher)[9]	MODERATE

Quality assessment						No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Indapamide versus HCTZ**	**Control**	**Relative**	**Absolute**	
SBP: 24 hour ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 7.5 higher (0 to 0 higher)[9]	MODERATE
DBP: 24h ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)										
1 (15)	RCTs	Serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	32	33	-	MD 2.0 higher (0 to 0 higher)[9]	MODERATE

ABPM – Ambulatory Blood Pressure Monitoring, DBP – diastolic blood pressure, HCTZ- hydrochlorothiazide, MD – mean difference, RCTs – randomised controlled trial(s), SBP – systolic blood pressure

[1] There were inadequate methodological information in two of the three trials

[2] Heterogeneity was 78%

[3] Heterogeneity was 76%

[4] Heterogeneity was 72%

[5] Heterogeneity 68%

[6] 1/2 studies unclear for allocation concealment

[7] 95% CI includes no effect and appreciable harm or benefit

[8] unclear allocation concealment

[9] There was NS difference between groups

Table 4. Results of studies / meta-analysis [Table 76 in NICE 2011 evidence review (9)**]**

Diuretic name (intervention)	Diuretic name (comparator)	Outcome measure and statistical significance (arm favoured)														Ref
		Change from baseline								End of follow-up				Absolute change		
		Supine		Upright		Seated		24h ABPM		Supine		Upright		Unclear method		
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	SBP	SBP	SBP	
Thiazide-like diuretic vs Thiazide diuretic																
CTD	HCTZ					NS	NS	NS								
IND	**HCTZ**	**SS (IND)**	**NS**	**SS (IND)**	**NS**	**NS**	**NS**	**NS**	**NS**	**SS* (IND)**	**SS* (IND)**	**SS* (IND)**	**SS* (IND)**			(11–17)
IND	BDZ									NS	NS	NS	NS	NS	NS	
Thiazide-like diuretic vs Thiazide-like diuretic																
IND	CTD	NS	NS							NS	NS					
Thiazide diuretic vs Thiazide diuretic																
HCTZ	BDZ	NS	NS	NS	NS											

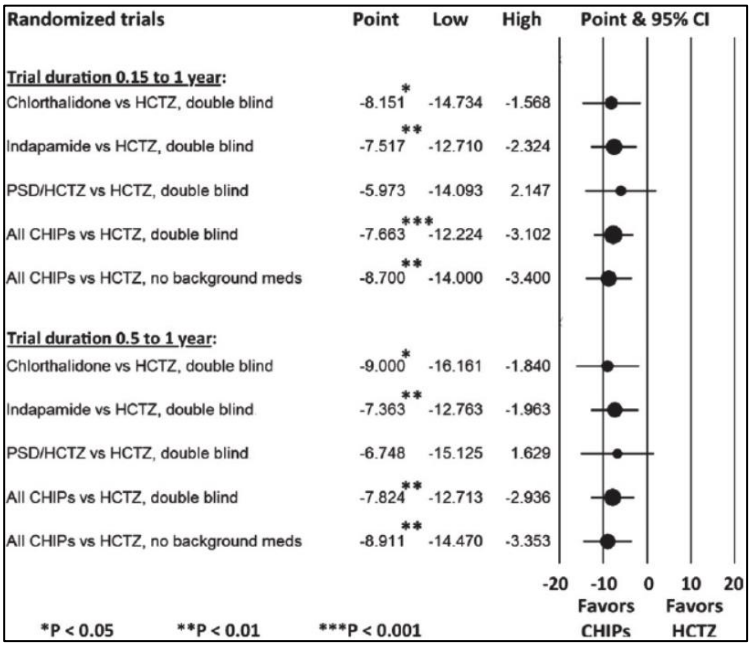
ABPM – Ambulatory Blood Pressure Monitoring, BDZ – bendroflumethiazide, CTD – chlorthalidone, DBP – diastolic blood pressure, HCTZ- hydrochlorothiazide, IND – indapamide, NS – not significant, SS – statistically significant, SBP – systolic blood pressure

*significant heterogeneity. Heterogeneity is removed if the Plante trial (11) is excluded from the analysis, and the overall effect becomes not significant. If a random effects model is applied to the pooled estimate, then the effect size also becomes not significant

B. <u>Roush et al 2018</u> (10) – ***AMSTAR II assessment: Moderate quality review***

- The analysis examined data for HCTZ, chlorthalidone, indapamide, triamterene/HCTZ, amiloride/HCTZ, spironolactone/HCTZ, spironolactone, eplerenone, or canrenone compared with another diuretic or one of the nondiuretic classes commonly used to treat hypertension. The study hypothesis was that 'CHIP' diuretics (CHlorthalidone, Indapamide, and Potassium-sparing diuretic/ HCTZ [PSD/HCTZ]) would reduce left ventricular mass (LVM) more than HCTZ. Left ventricular hypertrophy (LVH) is found in 36% - 41% of patients with hypertension and predicts cardiovascular events and total mortality independently of traditional risk. Among hypertensive patients, LVH contributes to about 30% of all deaths, 25% of cardiovascular events, and 75% of chronic heart failure (10).
- The review included studies with hypertensive patients with change in LVM or change in LVM indexed to height or to body surface area as outcomes.
- Thirty-eight RCTs were identified, with one RCT comparing indapamide with HCTZ and 37 comparing diuretics with non-diuretics (total of 2299 patients). The characteristics of the included studies are not reported in the review or its supplementary documents.
- Among the 38 RCTs, a 1% reduction in systolic blood pressure (SBP) predicted a 1% reduction in LVM, P = 0.00001.
- *HCTZ–indapamide comparisons of LVM reduction* (meta-analysis):
  - The difference between CHIP diuretics and HCTZ in reducing LVM varied substantially across trials (n=38) (heterogeneity), making interpretation uncertain. Double-blind trials (n=28) and trials with no background antihypertensive medications had no detectable heterogeneity, so analyses were limited to these trials. Among double-blind trials, there was no detectable publication bias.
  - Among the 28 double-blind trials, HCTZ reduced LVM (percent reduction [95% CI]) by -7.3 (-10.4, -4.2), P < 0.0001. Indapamide were superior to HCTZ by -7.5 (-12.7, -2.3), P=0.005. See figure 3.
  - The results indicate that indapamide reduce LVM 2-fold more than HCTZ among hypertensive patients.
  - The strength of evidence that CHIP diuretics surpass HCTZ for reducing LVM was high (GRADE criteria).
- *HCTZ–indapamide comparisons of reducing SBP and DBP* (meta-analysis):
  - There was no difference between CHIP diuretics and HCTZ: SBP -0.3 (-5.0, +4.3), DBP -1.6 (-5.6, +2.4)
  - There was some evidence of heterogeneity for the SBP and DBP comparisons for double-blind trials, but this did not achieve statistical significance.
  - Authors concluded that although blood pressure is generally related to LVM, it fails to explain the superiority of CHIP diuretics for reducing LVM.

Figure 2. Percent reduction in left ventricular mass from CHIP diuretics relative to HCTZ among trials where there was no detectable heterogeneity



Guidelines

Four relevant guidelines on the management of hypertension (with recommendations that include first-line use of thiazide diuretics) were identified. These guidelines were produced by Hypertension Canada, the National Insitute of Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the European Society of Cardiology and the European Society of Hypertension (ESC/ESH).

Three clinical guidelines (Hypertension Canada 2020, NICE 2011, ESC/ESH 2018) were appraised using the AGREE II tool (see Appendix G), and were found to have good quality of reporting. The references for these three guidelines, the relevant recommendations and selected items from the AGREE II appraisal outcome are presented in Table 5. Relevant recommendations made in the SIGN guideline [SIGN 149: Risk estimation and the prevention of cardiocascuar disease] are based on the NICE guideline presented in Table 5, so recommendations from SIGN 149 are not reported in this report.

Table 5. Clinical guideline quality assessments and recommendations

Citation	Recommendation	Strength of evidence	AGREE II*
Hypertension Canada. Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2020;36:596–624. (19)	*VIII. Choice of therapy for adults with hypertension without compelling indications for specific agents.* *A - Indications for drug therapy for adults with diastolic hypertension with or without systolic hypertension* Recommendations: - Initial therapy should be with either monotherapy or single-pill combination (SPC). - **Recommended monotherapy choices are: a) a thiazide/thiazide-like diuretic (Grade A), with longer-acting diuretics preferred (Grade B)**; b) a β-blocker (in patients younger than 60 years; Grade B); c) an ACE inhibitor (in non-black patients; Grade B); d) an ARB (Grade B); or e) a long-acting CCB (Grade B). - **Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).**	Grade A Grade B Grade C	Rigour of development: 72% Overall score: 92%
National Institute of Health and Care Excellence. Hypertension in adults: diagnosis and management (CG127). London; 2011 (20)	*1.6 Choosing antihypertensive drug treatment* *Step 1 treatment* Recommendations: - Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB. - Do not combine an ACE inhibitor with an ARB to treat hypertension. - Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. **If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic.** - **If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.** - **For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide.** - Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly: those with an intolerance or contraindication to ACE inhibitors and angiotensin II receptor antagonists or women of child-bearing potential or people with evidence of increased sympathetic drive. - If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes.		Rigour of development: 96% Overall score: 92%
Citation	**Recommendation**	**Strength of evidence**	**AGREE II***

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. (21)	*7.5.3 Drug treatment strategy for hypertension* Recommendations - Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CBs, and diuretics (thiazides and thiazide-like drugs such a chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. - Combination treatment is recommended for most hypertensive patients as initial therapy.	Class 1 Level A Class 1 Level A	Rigour of development: 79% Overall score: 67%

*AGREE II assessments are presented in Appendix G

A summary of the deliberations and recommendations from the three included clinical guidelines are presented below.

A. Hypertension Canada: Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children (2020) (19)

- Detailed information on the link from evidence to recommendations not provided
- Thiazides and thiazide-like diuretics recommended as monotherapy options (recommendation based on GRADE A evidence: RCTs or systematic reviews with high levels of internal validity and statistical precision), with preference stated for longer-acting diuretics, e.g. indapamide SR preparation (recommendation based on GRADE B evidence: RCTs, systematic reviews or prespecified subgroup analyses of RCTs that have lower precision or there is a need to extrapolate from studies).

B. NICE: Hypertension in adults: diagnosis and management (2004, updated 2006, 2011 and 2019) (20)

- During the 2011 update of the guideline, NICE changed its recommendations regarding the use of thiazides/thiazide-like diuretics as Step 1 therapy options. These recommendations remained unchanged in the 2019 guideline update.
- The guideline recommendations are stratified according to age and ethnicity (people aged under 55 years, people aged over 55 years and to black people of African or Caribbean family origin of any age), and it recommends that people be offered an angiotensin-converting enzyme (ACE) inhibitor, a low-cost angiotensin-II receptor blocker (ARB) or a calcium-channel blocker (CCB) under specified conditions, with thiazide-like diuretics only offered if a CCB is not suitable.
- The recommendations state a preference for thiazide-like diuretics, such as chlortalidone or indapamide, to conventional thiazide diuretics such as bendroflumethiazide or HCTZ, but include a statement that people who are already being treated with bendroflumethiazide or HCTZ and whose blood pressure is stable and well controlled should continue treatment with bendroflumethiazide or HCTZ.
- The guideline development group (GDG) used the NICE 2011 evidence review data presented above (see systematic reviews section), as well as the findings from another meta-analysis conducted as part of the guideline update [review question 8 (9)] , and made the following statements:
  - There were no direct comparisons between the different diuretics with regard to clinical outcomes.
  - Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. The guideline development group (GDG) found it difficult to reach firm conclusions regarding the comparative efficacy of different thiazide-type diuretics with regard to blood pressure lowering.
  - The GDG reviewed the clinical outcome studies with thiazide-type diuretics and found no direct comparator studies between different diuretics. Interpretation of data from head-to-head trials comparing diuretics with placebo or other antihypertensive drugs was complicated by the markedly different diuretic doses used across studies. The GDG noted that there was limited evidence confirming benefit of initial therapy on clinical outcomes with low doses of HCTZ (12.5-25mg o.d).
  - The evidence for the thiazide-like diuretics showed benefits of low dose indapamide or low dose chlorthalidone on a range of clinical outcomes. The evidence was derived from more contemporary studies that had more consistently used lower doses across studies (e.g. indapamide 1.5mg SR or 2.5mg o.d.) The GDG concluded that the consistency of the data suggested that the SR formulation was unlikely to have influenced the clinical outcomes in studies with indapamide.
  - Considering the data, the GDG found it difficult to recommend treatment with low dose thiazide-type diuretics, (e.g. bendroflumethiazide or HCTZ) for which there was no evidence of a benefit on clinical outcomes.
  - Consequently, the GDG recommended that when thiazide-type diuretics are used for the treatment for primary hypertension, thiazide-like diuretics should be preferred to conventional thiazide diuretics. The GDG did not consider it necessary to recommend that those people already treated with low dose thiazides and in whom blood pressure is controlled, should be switched to chlorthalidone or indapamide. However, when new diuretic therapy was to be initiated, then chlorthalidone or indapamide should be preferred.

C. ESC/ESH Guidelines for the management of arterial hypertension (2018) (21)

1. A new concept introduced in this version of the guideline is the preference for the use of two-drug combination therapy for the initial treatment of most people with hypertension, with a single-pill treatment strategy preferred. The use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic is proposed as the core treatment strategy for most patients, with beta-blockers used for specific indications.
2. No preference is stated for either thiazide or thiazide-like diuretics
3. The following statements relating to first-line therapy and thiazides are made in the guideline (21) and supplementary chapters (22):

   Combination therapy

   - A large number of randomized trials confirm that the main benefits of antihypertensive therapy are due to lowering of BP per se, largely independently of the drugs used to lower BP, but also that specific drug classes may differ in some effect or in special groups of patients (22).
   - "It can therefore be concluded that the major classes of antihypertensive agents—diuretics, beta blockers, calcium antagonists, ACE inhibitors, and ARBs—are suitable for the initiation and maintenance of antihypertensive therapy..." "Emphasis on identifying the first class of drugs to be used is probably outdated by the awareness that two or more drugs in combination are necessary in the majority of patients, particularly those with higher initial BPs or subclinical organ damage or associated diseases, in order to achieve target BP."(22)

   Conventional thiazides and thiazide-like diuretics

   - The lack of head-to-head RCTs testing the superiority of thiazide-like diuretics to conventional thiazide diuretics is noted.
   - The availability of studies showing cardiovascular benefits of thiazide-like diuretics is also discussed, noting that these agents are potentially more potent in lowering BP, have a longer duration of action compared with HCTZ, and lack evidence of greater incidence of side effects (18)
   - There is also more RCT evidence supporting the use of low dose thiazide-like diuretics compared to low dose conventional thiazide diuretics.
   - A recent meta-analysis of placebo-controlled studies based on thiazides, chlorthalidone and indapamide reported similar effects on CV outcomes for the three types of diuretics (18)
   - Therefore, in the absence of evidence from direct comparator trials and recognizing that many of the approved single-pill combinations (SPC) are based on HCTZ, the GDG recommended that thiazides, chlorthalidone, and indapamide can all be considered suitable antihypertensive agents.
4. Gaps in the evidence and need for further studies identified includes 'Outcome-based comparison between treatments based on thiazides vs thiazide-like diuretics'.

Summary of the clinical evidence

There were no direct comparisons between the different diuretics with regard to clinical outcomes. Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies (9). Another systematic review found that indapamide reduce left ventricular mass (LVM) 2-fold more than HCTZ in hypertensive patients, but it found no difference between the diuretics reviewed and HCTZ for systolic or diastolic blood pressure. Therefore, changes in blood pressure failed to explain the superiority of indapamide in reducing LVM.

The NICE 2011 guideline recommendation that thiazide-like diuretics are preferred over conventional thiazide diuretics is based on lack of evidence supporting use of conventional thiazide diuretics, not comparative efficacy. ESC/ESH guideline doesn't state preference for either conventional thiazide or thiazide-like diuretics - it recommends two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.

9. ALTERNATIVE AGENTS

Thiazide diuretics can be grouped into conventional thiazide diuretics (e.g. bendroflumethiazide and HCTZ), and thiazide-like diuretics (e.g. chlorthalidone and indapamide), so some of the evidence presented above included references to these medicines.

5. Bendroflumethiazide is not approved for use in South Africa.
6. Chlorthalidone is registered for use with SAHPRA, but only the 50mg tablet has a listed single exit price (SEP). Hygroton (chlortalidone 50mg) medicine SEP = R361.82 per 30 tablets (acquisition cost for one dosing unit = R12.06)

10. PHARMACEUTICAL COSTING AND BUDGET IMPACT DATA

Table 6. Pharmaceutical costs

	Intervention: Indapamide	**Intervention: Indapamide (SR)**	**Comparator: Hydrochlorothiazide (HCTZ)**
Pharmaceutical formulation	Tablet (standard)	Tablet (sustained release)	Tablet (standard)
Method of administration	Oral	Oral	Oral
Average dose/s and dosing schedule/s	One 2.5mg tablet once a day	One 1.5mg SR tablet once a day	One 25mg tablet once a day~
Average daily dose	1 x 2.5mg tablet	1 x 1.5mg tablet	1 x 25mg tablet
Dosing unit	1 tablet	1 tablet	1 tablet
Acquisition cost for one dosing unit (tablet)	R0,61	R4,31	R0,16
Total cost of treatment per month (30 days)	R18,30*	R129,30*	R4,80*
Total cost of treatment per year	R222,65	R1 573,15	R58,40
Estimated pharmaceutical acquisition costs for patient population newly initiated on thiazide diuretics (first-line therapy) in Year 1	R28 732 586	R203 012 207	R7 536 416
Additional annual acquisition costs compared to HCTZ *	R21 196 170	R195 475 791	-

~ 25mg HCTZ was selected as the most appropriate comparator for 2.5mg indapamide (dose equivalence)
*Annual cost assuming 100% market share for each intervention respectively - SEP database, 28 December 2020 (100% of SEP)

Budget impact analysis

Based on the following assumptions, the estimated budget impact of selecting indapamide 2,5mg for inclusion to the EML in the next five years will incur an additional annual cost of R10 598 085 in year 1 rising to R16 983 251 in year 5:

a) **Indapamide 2.5mg market share will be 50% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter.**
b) Only patients initiating first-line antihypertensive treatment are included (incidence only).
c) Only patients accessing public health care services are included.
d) Only 50% of the eligible population (newly diagnosed with essential hypertension) will seek treatment/be treated for hypertension.
e) HCTZ will not be appropriate for 5% of newly diagnosed hypertension patients (CCF, CKD, resistant hypertension, contra-indications).
f) Manufacturer price increases were not taken into account as tenders prices remain unchanged for 3+ years.

g) HCTZ 25mg is considered the most relevant comparator, as this is the technology most likely to be displaced by indapamide 2,5mg and is considered dose equivalent.
h) Health care resource use and adverse event costs have not been considered as they are assumed to be similar for indapamide (intervention) and HCTZ (comparator).

If only the first assumption (a) is changed (rest of the assumptions stay the same) to suggest that 100% of new patients initiated on antihypertensives are given indapamide 2.5mg as first-line treatment (instead of HCTZ), the additional annual pharmaceutical cost incurred will be R21 196 170 in year 1 rising to R23 199 916 in year 5.

See Appendix H for more detailed information about the budget impact analysis.

11.EQUITY CONSIDERATIONS

No significant impact on equity in health for marginalized groups were identified.

12.ACCEPTABILITY CONSIDERATIONS

There is variation in practice and preferences amongst health care professionals. Some clinicians have stated preference for indapamide over HCTZ, evidenced by prescribing patterns in the private health sector. There is a perception amongst clinicians that indapamide is more effective at controlling blood pressure, its pharmacokinetic properties allow for a better 24-hour therapeutic effect compared to HCTZ, and it's less likely to cause metabolic side-effects. Evidence supporting these theories are limited, but this might be due to the lack of high-quality studies investigating the long-term impact of thiazides. In the absence of evidence, clinicians rely on their practical observations, experience and recommendations from international guidelines and professional societies in treating patients with uncomplicated primary hypertension.

13.IMPLEMENTATION CONSIDERATIONS

No significant implementation considerations were identified.

14.EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty based on the NICE 2011 evidence review and report of blood pressure effects. Studies mainly report on the surrogate outcome, blood pressure. The studies were often of short duration, too small to provide robust data (underpowered), and there was also considerable variation in the doses of diuretics used in the various studies. Very limited data on long-term outcomes available.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ x None ☐	Blood pressure: Uncertain benefit potentially favouring indapamide with small, possibly not clinical meaningful, decreases in blood pressure (9,18) Left ventricular hypertrophy: Indapamide may reduce left ventricular mass 2-fold more than HCTZ among hypertensive patients, but the relation between this finding and blood pressure reduction is unclear (18).
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ x *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	One systematic review and network meta-analysis reported on metabolic outcomes for indapamide, HCTZ and chlorthalidone. The review was excluded as it was considered a critically low quality review.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☒ x	Indapamide and HCTZ were not detectably different in their effects on serum potassium, sodium, creatinine, glucose, cholesterol or uric acid (18).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ x	Uncertain desirable effect, no detectable difference in undesirable effects. On balance the evidence does not favour either the intervention or the comparison.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	Chlorthalidone discontinued from the South African market.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ x No ☐ Uncertain ☐	No significant implementation considerations were identified.
RESOURCE USE	**How large are the resource requirements?** More intensive ☒ x Less intensive ☐ Uncertain ☐	**Approximately 4-fold relative increase in costs for 1 year if the intervention were introduced.** **Price of medicines** - See detailed information above. **Estimated pharmaceutical cost for 1 year:** • Indapamide 2.5mg: R28 732 586,18

		• Indapamide SR 1.5mg: R203 012 207,29 • HCTZ 25mg: R7 536 416,05
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [x] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	Some health care professionals have stated their preference for indapamide over HCTZ, evidenced by prescribing patterns in the private health sector. Education about the evidence based will be needed to improve evidence based prescribing patterns.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	No significant impact on equity in health for marginalized groups were identified.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	16 July 2021	NT, MW, TL, TK	Indapamide not be recommended as first-line treatment of patients with uncomplicated hypertension. Indapamide is unaffordable, but may be considered for inclusion in the therapeutic interchange database as an alternative to HCTZ.
7.1	18 Aug 2022	NT, TL	Response to external comments

REFERENCES

1. National Department of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa | Primary Healthcare Level 2020 Edition. 2020.
2. Republic of South Africa. Essential Drugs Programme. Hospital Level (Adults) Standard Treatment Guidelines and Essential Medicines List. Pretoria: National Department of Health; 2019.
3. The National Department of Health South Africa, Statistics South Africa, South African Medical Research Council, et al. South Africa Demographic and Health Survey 2016 | Chapter 16 - Adult Morbidity. Pretoria, South Africa and Rockville, Maryland, USA; 2019.
4. National Department of Health. Strategic Plan 2020/21 - 2024/25 [Internet]. 2020. Available from: http://www.health.gov.za/wp-content/uploads/2020/11/depthealthstrategicplanfinal2020-21to2024-25-1.pdf
5. Sanele M, Shamagonam J, Sewpaul R, Madela S, Reddy P. Early detection, care and control of hypertension and diabetes in South Africa: A community-based approach. African J Prim Heal care Fam Med. 2020;12(1):9 pages.
6. South African Health Products Regulatory Authority. Registered health products [Internet]. [cited 2021 May 19]. Available from: https://www.sahpra.org.za/registered-health-products/
7. Essential Drugs Programme. Master Health Product List - May 2021 [Internet]. 2021. Available from: http://www.health.gov.za/tenders/
8. PHARMA DYNAMICS (PTY) LTD. Package insert for Dyna Indapamide SR [Internet]. Cape Town; 2011. Available from: http://www.sahpra.org.za/wp-content/uploads/2020/04/Dyna-Indapamide-SR_PI_PHARMA-DYNAMICS_MCC-Format-25-November-2011.pdf
9. National Clinical Guideline Centre at The Royal College of Physicians. The clinical management of primary hypertension in adults | Clinical Guideline 127 Methods, evidence, and recommendations. London; 2011.
10. Roush GC, Ramy A, Song S, Ernst ME, Sica DA, Kostis JB. Hydrochlorothiazide vs chlorthalidone, indapamide, and potassium-sparing/hydrochlorothiazide diuretics for reducing left ventricular hypertrophy: A systematic review and meta-analysis. J Clin Hypertens. 2018;20:1507–15.
11. Plante G, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. Curr Med Res Opin. 1983;8(Suppl 3):59–66.
12. Kreeft J, Langlois S, Ogilvie R. Comparative trial of indapamide and hydrochlorothiazide in essential hypertension, with forearm plethysmography. J Cardiovasc Pharmacol. 1984;6(4):622–6.
13. Plante G, Dessurault D. Hypertension in elderly patients. A comparative study between indapamide and hydrochlorothiazide. Am J Med. 1988;84(1B):98–103.
14. Spence J, Huff M, Barnett P. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. Can J Clin Pharmacol. 2000;7(1):32–7.
15. Brandao S, Izar C, Fischer S, Santos A, Monteiro C, Povoa R, et al. Early increase in autoantibodies against human oxidized low-density lipoprotein in hypertensive patients after blood pressure control. Am J Hypertens. 2010;23(2):208–14.
16. Emeriau J, Knauf H, Pujadas J, Calvo-Gomez C, Abate G, Leonetti G, et al. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens. 2001;19(2):343–50.
17. Elliott W, Weber R, Murphy M. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. J Clin Pharmacol. 1991;31(8):751–7.
18. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone Antihypertensive and Metabolic Effects. Hypertension. 2015;65:1041–6.
19. Hypertension Canada. Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2020;36:596–624.
20. National Institute of Health and Care Excellence. Hypertension in adults: diagnosis and management (CG127). London; 2011.
21. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH Guidelines for the management of arterial

hypertension. Eur Heart J. 2018;39:3021–104.
22. Burnier M, Kjeldsen S, Heagerty A, Williams B. ESC CardioMed (3 edn): Drug treatment of hypertension. Camm AJ, Lüscher TF, Maurer G, Serruys PW, editors. ESC CardioMed. 2018. 1–43 p.
23. Krum H, Skiba M, Gilbert R. Comparative metabolic effects of hydrochlorothiazide and indapamide in hypertensive diabetic patients receiving ACE inhibitor therapy. Diabet Med. 2003;20:708–12.
24. Madkour H, Gadallah M, Riveline B, Plante G, Massry S. Comparison between the effects of indapamide and hydrochlorothiazide on creatinine clearance in patients with impaired renal function and hypertension. Am J Nephrol. 1995;15:251–5.
25. Radevski I., Valtchanova Z., G.P C, A.M W, Ngcezula T, Sareli P. Comparison of indapamide and low-dose hydrochlorothiazide monotherapy in black patients with mild to moderate hypertension. S Afr Med J. 2002;92:523–53.
26. Bhigjee A., Seedat YK, Hoosen S, Neerahoo R., Naidoo K. Biochemical changes in Black and Indian hypertensive patients on diuretic therapy. S Afr Med J. 1983;64:969–72.
27. Malini P., Strocchi E., Ricci C., Ambrosinioni E. Indapamide or hydrochlorothiazide in hypertensive patients resistant to treatment with an angiotensin-converting enzyme inhibitor. Curr Ther Res. 1994;55:932–7.
28. Zhang X, Zhao Q. Association of Thiazide-Type Diuretics With Glycemic Changes in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. J Clin Hypertens. 2016;18(4):342–51.
29. Olde Engberink R, Frenkel W, Van den Bogaard B, Brewster L, Vogt L, Van den Born B. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis. Hypertension. 2015;65(5):1033–40.
30. Liang W, Ma H, Cao L, Yan W, Yang J. Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-analysis. J Cell Mol Med. 2017;21(11):2634–42.

APPENDIX A: REGISTERED INDAPAMIDE PREPARATIONS AVAILABLE IN SOUTH AFRICA [SAHPRA (6)]

Registration number	Registered	Proprietary name	Dosage form	Manufacturer	Ingredients	Pack size	Single Exit Price (ZAR)	
							Pack	Unit
32/7.1.3/0406	2/7/2001	Catexan	Tablet	Biogaran South Africa (PTY) LTD	Indapamide 2,5 mg	30 tablets	18,30	0,61
G/7.1/65	7/26/1974	Natrilix*	Tablet	Servier Laboratories SA (PTY) LTD	Indapamide 2,5 mg	30 tablets	18,84	0,63
30/7.1/0092	2/8/1996	Adco-dapamax	Tablet	Adcock Ingram LIMITED	Indapamide 2,5 mg	30 tablets	18,90	0,63
						600 tablets	378,00	0,63
31/7.1/0099	2/21/1997	Daptril	Tablet	FDC SA (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,29	0,64
						600 tablets	385,98	0,64
29/7.1/0590	12/20/2002	Mylan indapamide 2,5	Tablet	Mylan (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,47	0,65
31/7.1/0097	6/28/1997	Cipla-indapamide	Tablet	Cipla Medpro (PTY) LTD	Indapamide 2,5 mg	30 tablets	19,69	0,66
Z/7.1/203	10/11/1993	Sandoz indapamide 2,5	Tablet	Zimbili Pharma CC, RSA	Indapamide 2,5 mg	30 tablets	26,04	0,87
29/7.1/0266	4/1/1996	Hydro-less	Tablet	Litha Pharma (PTY) LTD	Indapamide 2,5 mg	30 tablets	22,74	0,76
						600 tablets	345,36	0,58
31/7.1/0670	4/14/1998	Indalix	Tablet	Pharmacare LIMITED	Indapamide 2,5 mg	30 tablets	36,65	1,22
						600 tablets	411,98	0,69
31/7.1/0098	6/28/1997	Rilix	Tablet	Xeragen Laboratories (PTY) LTD	Indapamide 2,5 mg	Not available		
35/7.1/0179	11/25/2005	Dinatrix	Tablet	Pharmacare LIMITED	Indapamide 2,5 mg	Not available		
31/7.1/0166	5/2/1997	Natrilix SR	Tablet	Servier Laboratories SA (PTY) LTD	Indapamide 1,5 mg	30 tablets	129.28	4,31

APPENDIX B: REGISTERED HYDROCHLOROTHIAZIDE PREPARATIONS AVAILABLE ON TENDER [MASTER HEALTH PRODUCT LIST – MAY 2021]

Registration number	Registered	Proprietary name	Dosage form	Manufacturer	Ingredients	Pack size	Tender Price (ZAR)	
							Pack	Unit
A39/18.1/0399	9/23/2005	Ridaq Tab 12.5mg 28's	Tablet	Pharmacare Limited	Hydrochlorothiazide 12,5mg	28 tablets	4,1	0,15
M/18.1/35	1/28/1981	Ridaq Tabs 25mg 28's BB	Tablet	Pharmacare Limited	Hydrochlorothiazide 25mg	28 tablets	4,35	0,16
To find		Hydrochlorothiazide 25 Ascendis	Tablet	Dezzo Trading 392 (Pty) Ltd	Hydrochlorothiazide 25mg	28 tablets	4,61	0,16
To find		Gulf Hydrochlorothiazide 25	Tablet	Gulf Drug Company (Pty) Ltd	Hydrochlorothiazide 25mg	28 tablets	4,58	0,16

APPENDIX C: SEARCH STRATEGY

Title: Thiazide – Like Diuretics Compared to Thiazide Diuretics in Patients with Essential Hypertension
Database: CENTRAL (Issue 3 of 12, March 2021) & CLIB (Issue 4 of 12, April 2021)
Date: 29 April 2021

ID	Search	Hits
#1	[mh hypertension] or hypertens*:ti,ab (Word variations have been searched)	58898
#2	(high or rais* or rising OR increas* or elevat* or lower) near/3 ("blood pressure" or "diastolic pressure" or "systolic pressure" or "arterial pressure"):ti,ab (Word variations have been searched)	16172
#3	(high or rais* or rising OR increas* or elevat* or lower) near/4 (bp or dbp or hbp or sbp):ti,ab (Word variations have been searched)	6233
#4	#1 or #2 or #3	68974
#5	[mh indapamide] or indapamide:ti,ab,kw or metindamide:ti,ab,kw or lozol:ti,ab,kw (Word variations have been searched)	664
#6	[mh Hydrochlorothiazide] or Hydrochlorothiazide:ti,ab,kw or microzide:ti,ab,kw or esidrix:ti,ab,kw or maxzide:ti,ab,kw or dichlothiazide:ti,ab,kw or oretic:ti,ab,kw or esidrex:ti,ab,kw OR hypothiazide:ti,ab,kw (Word variations have been searched)	3984
#7	#4 and #5 and #6	75
#8	("thiazide-like" or thiazide) near/3 diuretic*:ti,ab,kw	937
#9	#4 and #8	724
#10	#7 or #9 in Cochrane Reviews	14
#11	#7 or #9 in Trials	770

Title: Thiazide – Like Diuretics Compared to Thiazide Diuretics in Patients with Essential Hypertension
Database: PubMed
Date: 29 April 2021

Search	Query	Results
#12	Search: (#7 OR #9) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review Sort by: Most Recent	46
#10	Search: #7 OR #9 Sort by: Most Recent	2,428
#9	Search: #4 AND #8 Sort by: Most Recent	2,322
#8	Search: ("Thiazide-like"[tiab] OR thiazide[tiab]) AND diuretic*[tiab] Sort by: Most Recent	3,547
#7	Search: #4 AND #5 AND #6 Sort by: Most Recent	170
#6	Search: Hydrochlorothiazide[mh] OR Hydrochlorothiazide*[tiab] OR microzide[tiab] OR esidrix[tiab] OR maxzide[tiab] OR dichlothiazide[tiab] OR oretic[tiab] OR esidrex[tiab] OR hypothiazide[tiab] Sort by: Most Recent	9,190
#5	Search: indapamide[mh] OR indapamide*[tiab] OR metindamide*[tiab] OR lozol[tiab] Sort by: Most Recent	1,399
#4	Search: #1 OR #2 OR #3 Sort by: Most Recent	731,354
#3	Search: (High[tiab] OR rais*[tiab] OR rising[tiab] OR increas*[tiab] OR elevat*[tiab] OR lower[tiab]) AND (bp[tiab] OR dbp[tiab] OR hbp[tiab] OR sbp[tiab]) Sort by: Most Recent	99,280
#2	Search: (High[tiab] OR rais*[tiab] OR rising[tiab] OR increas*[tiab] OR elevat*[tiab] OR lower[tiab]) AND (blood pressure[tiab] OR diastolic pressure[tiab] OR systolic pressure[tiab] OR arterial pressure[tiab]) Sort by: Most Recent	261,076
#1	Search: Hypertension[mh] OR hypertens*[tiab] Sort by: Most Recent	521,426

APPENDIX D: EVALUATING THE METHODOLOGICAL QUALITY OF SYSTEMATIC REVIEWS - AMSTAR 2 TOOL

	NICE 2011 evidence review (9) – **Moderate quality review**	Yes/ Partial Yes/ No
No.	**Criteria**	**Consensus**
1	Did the research questions and inclusion criteria for the review include the components of PICO?	**Yes**
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**Partial Yes**
3	Did the review authors explain their selection of the study designs for inclusion in the review?	**Yes**
4	Did the review authors use a comprehensive literature search strategy?	**Partial Yes**
5	Did the review authors perform study selection in duplicate?	**Yes**
6	Did the review authors perform data extraction in duplicate?	**Yes**
7	Did the review authors provide a list of excluded studies and justify the exclusions?	**No**
8	Did the review authors describe the included studies in adequate detail?	**Yes**
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	**Partial Yes**
10	Did the review authors report on the sources of funding for the studies included in the review?	**No**
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	**Yes**
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	**Yes**
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	**Yes**
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	**Yes**
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	**No**
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Yes**

	ROUSH 2018 (10) – Moderate quality review	Yes/ Partial Yes/ No
No.	**Criteria**	**Consensus**
1	Did the research questions and inclusion criteria for the review include the components of PICO?	**Yes**
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**Yes**
3	Did the review authors explain their selection of the study designs for inclusion in the review?	**Yes**
4	Did the review authors use a comprehensive literature search strategy?	**Yes**
5	Did the review authors perform study selection in duplicate?	**Yes**
6	Did the review authors perform data extraction in duplicate?	**Yes**
7	Did the review authors provide a list of excluded studies and justify the exclusions?	**No**
8	Did the review authors describe the included studies in adequate detail?	**No**
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	**Partial Yes**
10	Did the review authors report on the sources of funding for the studies included in the review?	**No**
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	**Yes**
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	**Yes**
13	Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	**Yes**
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	**Yes**
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	**Yes**
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Yes**

APPENDIX E: SYSTEMATIC REVIEWS EXCLUDED AFTER FULL TEXT SCREENING

Author, date	Type of study	Reason for exclusion
Roush 2015 (18)	Systematic review	The systematic review and meta-analysis of head-to-head randomized controlled trials investigated how HCTZ compares with indapamide in terms of antihypertensive and metabolic effects. The review had a similar scope to the NICE 2011 evidence review (findings included in this medicine review), but included some additional studies excluded from the NICE 2011 evidence review. These additional studies were focused on more restrictive populations [diabetic patients (23), chronic kidney disease (24), excluded insulin-dependent patients (25)], had different outcome measures [metabolic changes (26)], or included patients receiving concomitant baseline treatments [enalapril at baseline (27)]. Findings from Roush 2015 are not presented in this medicine review after AMSTAR assessment indicated it to be of critically low quality and seeing that its scope significantly overlaps with NICE 2011 evidence review (which was assessed to be a review of moderate quality). Roush 2015 provided some information on metabolic outcomes (no significant difference between indapamide and HCTZ).
Zhang 2016 (28)	Systematic review	The review aimed to assess to the effects of thiazide-type diuretics on glycaemic metabolism in hypertensive patients. Studies included in the review included monotherapy and combination therapy regimes.
Olde Engberink 2015 (29)	Systematic review	The review investigated the effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality. Studies included in the review included monotherapy and combination therapy regimes. HCTZ were mostly given as part of combination therapy.
Liang 2017 (30)	Systematic review	The authors summarized the existing evidence on the two types of drugs and conducted a meta-analysis on their efficacy in lowering blood pressure and effects on blood electrolyte, glucose, and total cholesterol. Studies included in the review included monotherapy and combination therapy regimes.

APPENDIX F: CHARACTERISTICS OF HEAD-TO-HEAD RCTS (INDAPAMIDE/HCTZ COMPARISON ONLY) INCLUDED IN NICE 2011 EVIDENCE REVIEW

Authors (year)	N	Population	Intervention	Comparator	Design	Outcomes measured	Results
Kreeft, 1984 (12)	17	Patients 34-66 years in age with uncomplicated essential hypertension	Indapamide 2.5mg/day	HCTZ (50mg/day)	Randomized, placebo-controlled, double-blind cross-over study 2 months placebo run-in, 12 weeks thiazide diuretic drug, 2 months placebo washout, 12 weeks alternate thiazide diuretic drug	Standing systolic/diastolic pressure Orthostatic changes in mean pressure and heart rate Serum potassium, serum uric acid and cholesterol.	No significant difference in blood pressure between groups. Similar changes in serum potassium, serum uric acid and cholesterol.
Plante, 1988 (13)	47	Elderly hypertensive patients (ages 65 to 91)	Indapamide 2.5mg/day	HCTZ (50mg/day)	Randomized 6-week placebo-treatment period, followed by 48 weeks active therapy	Blood pressure and serum chemistry	Indapamide better for reduced blood pressure (no P value reported) and was less likely to be associated with hyponatremia and hypokalaemia.
Plante, 1983 (11)	24	Patients with mild arterial hypertension	Indapamide 2.5mg/day	HCTZ (50mg/day)	Double-blind, controlled 4-6 week washout placebo period, followed by 12 weeks active therapy.	Blood pressure and pulse rate in the recumbent and upright positions. Laboratory measurements of plasma electrolytes, other biochemical and haematological parameters.	Indapamide better for reduction in diastolic blood pressure in the recumbent position. Some significant changes in plasma electrolytes (both groups) and serum uric acid (HCTZ group) but none of clinical importance
Spence, 2000 (14)	39	Patients with mild to moderate hypertension	Indapamide 2.5mg/day	HCTZ (25mg/day)	Randomized, double-blind 6 months	Blood pressure Potassium and chloride Plasma total cholesterol, high density lipoprotein, apolipoprotein A1, apolipoprotein B, triglycerides. Plasma glucose	No significant difference in blood pressure between groups No significant differences in the reduction of potassium and chloride Neither drug was associated with a significant change in plasma total cholesterol, high density lipoprotein, apolipoprotein A1, apolipoprotein B or the ratio of total cholesterol to HDL levels. Triglyceride levels increased significantly more with indapamide than with HCTZ (P=0.02). Neither drug affected plasma glucose.

Authors (year)	N	Population	Intervention	Comparator	Design	Outcomes measured	Results
Brandao, 2010 (15)	94	Patients recently diagnosed hypertension on stage 1, with no other risk factors, and naive of antihypertensive medication	Indapamide 1.5mg/day (SR)	HCTZ (25mg/day)	Randomized 12 weeks. Addition of ACE inhibitor at 6 weeks if target BP not met.	Antioxidized low-density lipoprotein antibodies Office-based and 24-h ambulatory blood pressure measurements	No significant difference in blood pressure (office or 24-h ambulatory blood pressure) between groups
Emeriau, 2001 (16)	524	Elderly hypertensive patients (mean age: 72.4 years)	Indapamide 1.5mg/day (SR)	HCTZ (25mg/day) Amlodipine (5 mg/day)	Randomized, double-blind, controlled 4-week washout placebo period; 12 weeks treatment	Clinic systolic and diastolic blood pressure variations	Similar reduction in blood pressure between groups (equivalence test)
Elliot, 1991 (17)	11	Hypertensive patients with serum uric acid concentrations greater than 8.0 mg/dL while receiving previous therapy with thiazides	Indapamide 2.5mg/day or HCTZ (25 mg/day)	Placebo (lactose)	Double-blind, randomized, placebo-controlled, double-crossover 28 days	Supine and standing blood pressures, weight, pulse rates and sera	No significant difference in blood pressure between groups. Urate concentration with indapamide was significantly lower than that with HCTZ ($p<0.02$), but the magnitude of the difference was small.

APPENDIX G: EVALUATING THE METHODOLOGICAL QUALITY OF CLINICAL GUIDELINES – AGREE II

Hypertension Canada: 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children

AGREE II assessment scores																								
Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	6	7	6	5	6	7	6	2	6	6	6	5	6	7	6	6	7	7	4	6	7	7	7
Appraiser 2	7	7	7	7	4	7	5	6	3	7	5	1	7	7	7	4	7	5	3	3	5	7	7	6
Item total	14	13	14	13	9	13	12	12	5	13	11	7	12	13	14	10	13	12	10	7	11	14	14	13
Domain total	41			35			85								37			40				28		13
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**97**			**81**			**72**								**86**			**67**				**100**		**92**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{axumim possible score - minimum possible sco}} \times 100$$

NICE: Hypertension - The clinical management of primary hypertension in adults (CG127)

AGREE II assessment scores																								
Hypertension: The clinical management of primary hypertension in adults (CG127)																								
Scoring the guidelines																								
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	6	7	7	6	7	6	7	7	6	7	6	7	7	6	7	7	7	7	7	7
Appraiser 2	7	7	7	7	7	7	7	7	7	7	7	7	6	7	7	7	7	4	5	7	5	6	6	6
Item total	14	14	14	14	13	14	14	13	14	13	14	14	12	14	13	14	14	10	12	14	12	13	13	13
Domain total	42			41			108								41			48				26		13
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**100**			**97**			**96**								**97**			**83**				**92**		**92**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{laxumim possible score - minimum possible sco}} \times 100$$

2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension

AGREE II assessment scores																							
2018 ESC/ESH Guidelines for the management of arterial hypertension																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	6	7	4	1	7	4	4	4	5	5	5	4	6	7	7	7	6	7	1	3	4	5	4
Appraiser 2	7	7	6	7	3	6	7	7	6	7	7	7	7	7	7	7	7	4	7	3	7	7	7	6
Item total	14	13	13	11	4	13	11	11	10	12	12	12	11	13	14	14	14	10	14	4	10	11	12	10
Domain total	40			28			92								42			38				23		10
Minimum possible score	6			6			16								6			8				4		2
Maxumim possible score	42			42			112								42			56				28		14
Domain score	**94**			**61**			**79**								**100**			**63**				**79**		**67**

Overall assessment: I would recommend this guideline for use - adapted for local context

Score: (e.g. domain 1)
Maximum possible score= 7 (highest score) X no of items X 2 appraisers
Minimum possible score= 1 (lowest score) X no of items X 2 appraisers

Score for each domain:

$$\frac{\text{obtained score - minimum possible score}}{\text{maxumim possible score - minimum possible sco}} \times 100$$

APPENDIX H: PHARMACEUTICAL BUDGET IMPACT ANALYSIS

This budget impact analysis presents the relative acquisition costs of indapamide and HCTZ for consideration in addition to the evidence of the relative clinical effect.

Technology under review: Indapamide

Description		**Source**
Acquisition cost per annum	R222.65	Single exit price for lowest indapamide 2.5mg tablet (Catexan)
Method of administration	Oral	Prescribing information
Dosage	2.5mg once a day	Prescribing information
Average length of a course of treatment	Ongoing (chronic)	Prescribing information
Dose adjustments	Not applicable	Prescribing information

Table adapted from the NICE budget impact analysis template

HCTZ 25mg is considered the most relevant comparator, as this is the technology most likely to be displaced by Indapamide and is considered dose equivalent.

Uptake and market share

Five-year estimates for the following implementation scenarios are provided:

1. Status Quo: No change with all eligible patients receiving HCTZ
2. Rapid adoption of indapamide: Indapamide 2.5mg market share will be 50% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter
3. Slow adoption of indapamide: Indapamide 2.5mg market share will be 25% of patients initiated on first-line antihypertensives in first year, with growth of 10% each year thereafter

Market share for indapamide and HCTZ for all eligible patients receiving first line antihypertensive treatment each year

Scenario	**Treatment**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Status Quo: existing treatment(s) only	Indapamide	0%	0%	0%	0%	0%
	HCTZ	100%	100%	100%	100%	100%
Rapid Adoption Scenario	Indapamide	50,00%	55,00%	60,50%	66,55%	73,21%
	HCTZ	50,00%	45,00%	39,50%	33,45%	26,80%
Slow Adoption Scenario	Indapamide	25,00%	27,50%	30,25%	33,28%	36,60%
	HCTZ	75,00%	72,50%	69,75%	66,73%	63,40%

Eligible population

The eligible patient population has been calculated under the following assumptions:

- Only patients newly initiated on first-line antihypertensive treatment are included (incidence only).
- Only patients accessing public health care services are included (84% of SA population).
- Only 50% of the eligible population (newly diagnosed with essential hypertension) will seek treatment for hypertension.
- HCTZ will not be appropriate for 5% of newly diagnosed hypertension patients (CCF, CKD, resistant hypertension, contra-indications).

Resources

Health care resource use and adverse event costs have not been considered in this budget impact analysis as they are assumed to be the similar for indapamide (intervention) and HCTZ (comparator).

Drug acquisition costs for indapamide and HCTZ

Cost type	Cost (ZAR)*	Unit
Indapamide 2.5mg	R222.65	Per person for one year
Indapamide 1.25mg	R1 573.15	Per person for one year
HCTZ 25mg	R58.40	Per person for one year

*SEP database, 28 December 2020 (100% of SEP)

Manufacturer price increases were not considered in this budget impact analysis.

Estimates of annual budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Rapid adoption implementation scenario					
Indapamide acquisition costs	R14 366 293	R16 163 272	R18 185 407	R20 460 958	R23 021 741
HCTZ acquisition costs	R3 768 208	R3 468 720	R3 114 260	R2 697 517	R2 210 249
Total acquisition costs	*R18 134 501*	*R19 631 992*	*R21 299 667*	*R23 158 475*	*R25 231 990*
Slow adoption implementation scenario					
Indapamide acquisition costs	R7 183 146	R8 081 636	R9 092 703	R10 230 479	R11 510 870
HCTZ acquisition costs	R5 652 312	R5 588 493	R5 499 231	R5 380 921	R5 229 494
Total acquisition costs	*R12 835 458*	*R13 670 129*	*R14 591 935*	*R15 611 400,*	*R16 740 364*
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with rapid adoption of the new technology	R10 598 085	R11 923 725	R13 415 464	R15 094 150	R16 983 251
> In a market with slow adoption of the new technology	R5 299 042	R5 961 862	R6 707 732	R7 547 075	R8 491 625

Additional analyses

1. Change in market share assumptions: all eligible patients are switched to indapamide in year 1

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Complete switch to indapamide implementation scenario					
Indapamide acquisition costs	R28 732 586	R29 387 768	R30 058 524	R30 745 242	R31 448 317
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with complete switch from HCTZ to Indapamide	R21 196 170	R21 679 501	R22 174 321	R22 680 916	R23 199 578

2. Variation in cost of indapamide (acquisition cost of indapamide is reduced by 40%)

	Year 1	Year 2	Year 3	Year 4	Year 5
Patient population that could potentially receive the new technology	**129 048**	**131 991**	**135 003**	**138 088**	**141 246**
Status quo implementation scenario					
HCTZ acquisition costs	R7 536 416	R7 708 267	R7 884 203	R8 064 325	R8 248 739
Rapid adoption implementation scenario					
Indapamide acquisition costs	R8 619 775	R9 697 963	R10 911 244	R12 276 575	R13 813 044
HCTZ acquisition costs	R3 768 208	R3 468 720	R3 114 260	R2 697 517	R2 210 249
Total acquisition costs	*R12 387 983*	*R13 166 683*	*R14 025 504*	*R14 974 092*	*R16 023 294*
Slow adoption implementation scenario					
Indapamide acquisition costs	R4 309 887	R4 848 981	R5 455 622	R6 138 287	R6 906 522
HCTZ acquisition costs	R5 652 312	R5 588 493	R5 499 231	R5 380 921	R5 229 494
Total acquisition costs	*R9 962 199*	*R10 437 475*	*R10 954 854*	*R11 519 209*	*R12 136 016*
NET PHARMACEUTICAL BUDGET IMPACT *(future - current treatment pathway costs)*					
> In a market with rapid adoption of the new technology	R4 851 567	R5 458 416	R6 141 301	R6 909 766	R7 774 555
> In a market with slow adoption of the new technology	R2 425 783	R2 729 208	R3 070 650	R3 454 883	R3 887 277

Date: 21 July 2022

Response to external comments on the HCTZ vs indapamide review

Hydrochlorothiazide (HCTZ) is the first line (monotherapy) pharmacological treatment for uncomplicated hypertension recommended in the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) for South Africa. In the past HCTZ has been used successfully in the South African clinical landscape with minimal adverse metabolic effects in the majority of uncomplicated hypertensive patients.

When compared to indapamide, HCTZ is suggested to have limited efficacy. However, much of the available published data is suboptimal and does not compare these two agents on a head-to-head design with hard clinical outcomes. The current positions taken by some clinical guidelines to prefer thiazide-like diuretics over thiazide diuretics is largely based on the presumed improved BP lowering effect and favourable side effect profile, rather than on comparative efficacy. While other studies have investigated comparative efficacy of HCTZ and chlorthalidone, these have not been considered as chlorthalidone is not available in South Africa.

Due to the inconclusive evidence the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines do not state preference for either conventional thiazide or thiazide-like diuretics – instead these guidelines recommend two-drug combination therapy for the initial treatment of most people with hypertension, and thiazides are recommended as part of that combination therapy. The Hypertension Canada 2020 and the International Society of Hypertension guideline recommended both thiazide and thiazide-like diuretics as monotherapy choices, with preference for longer-acting diuretics stated.

Current evidence supporting the use of indapamide over HCTZ is of low quality with uncertain impact on important clinical outcomes. In addition, indapamide is almost four times more expensive than HCTZ and a large South African patient population would be eligible to receive the treatment each year. Including indapamide as a first-line treatment option will therefore have a significant impact on the pharmaceutical budget, while its additional clinical impact is uncertain. The Expert Review Committee therefore does not support the introduction of indapamide as a first line agent. Furthermore, with increasing awareness of the benefits of upfront combination therapy in appropriately risk stratified hypertensives, the case for changing first line monotherapy is now less compelling.