**SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST**
**CHAPTER 8: ENDOCRINE DISORDERS**
**NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 - 2019)**

**Medicine amendment recommendations, with supporting evidence and rationale are listed below.**
**Kindly review the medicine amendments in the context of the endocrine chapter.**

| SECTION | MEDICINE | ADDED/DELETED/AMENDED |
|---|---|---|
| **8.2 Adrenal insufficiency (Addison disease)** | | |
| *- Investigations* | ACTH depot, IM | Dose retained at "1 mg" |
| *- Severe stress* | Hydrocortisone, IV | Dose retained at "100 mg 6 hourly" |
| **8.3 Androgen deficiency** | Testosterone cypionate, IM | Dosing not amended; directions for use amended |
| **8.5 Diabetes mellitus** | | |
| *- Diagnosis* | HbA1C | Not added for diagnosing diabetes mellitus |
| | Oral glucose tolerance test | Added |
| *- Monitoring* | Urine protein monitoring by dipstick | Baseline and annual monitoring added |
| | Serum lipids | Annual monitoring not added |
| **8.5.1 Type 2 Diabetes mellitus** | Glimepiride, oral | Maximum dose added |
| | Gliclazide, slow release oral | Not added |
| | Glucagon-like peptide 1 receptor agonist (GLP1 RA), oral | Not added |
| | Sodium glucose transporter 2(SGLT2) inhibitor, oral | Not added |
| | Dipeptidyl-peptidase-4 (DPP4) inhibitor, oral | Not added |
| | Pioglitazone, oral | Not added |
| **8.5.1 Type 1 Diabetes mellitus** | Long-acting insulin analogues | Not added |
| | Home glucose monitoring | Amended |
| **8.6.1 Hypoglycaemia (In hospital)** | Dextrose 50%, IV | Retained |
| | Glucagon, IM | Deleted |
| **8.7.1 Diabetic neuropathies** | Amitriptyline, oral | Deleted (Moved to pain chapter) |
| | Paracetamol, oral | Deleted (Moved to pain chapter) |
| | Carbamazepine, oral | Deleted (Moved to pain chapter) |
| **8.8 Dyslipidaemia** | HMGCoA reductase inhibitors | Indication extended to include CKD and microalbuminuria |
| *- Primary prevention of ischaemic events* | Simvastatin, oral | Dose retained as 10 mg |
| *- Secondary prevention of ischaemic events* | Simvastatin, oral | Dose amended from low 10 mg dose to intermediate 40 mg dose |
| *- Secondary prevention of ischaemic events: i) Drug-drug interaction with amlodipine* | Simvastatin, oral 10-20 mg | Added |
| *- Secondary prevention of ischaemic events: ii) Drug-drug interaction with protease inhibitors* | Atorvastatin, oral, 10 mg | Added |
| *- Secondary prevention of ischaemic events: iii) Managing ADRs associated with intermediate dose statins* | Simvastatin, oral, 10 mg | Added |
| - CVD risk assessment | Screening of IHD risk using BMI | Added |
| | Screening of IHD risk using Framingham tables | Retained |
| **8.9 Hypercalcaemia, including primary hyperparathyroidism** | Bisphosphonates, IV | Recommended as a therapeutic class; dose adjustment added for renal impairment |
| | Pamidronic acid, IV | Deleted from STG, as discontinued from market (but retained on therapeutic interchange database) |
| | Zoledronic acid, IV | Added as an example of therapeutic class – listed in STG |
| | Ibandronic acid, IV | Added as a therapeutic alternative |

| | | |
|---|---|---|
| **8.10 Hypocalcaemia** | Calcium gluconate 10%, infusion | Dosing amended |
| **8.12 Osteoporosis** | | |
| - *Primary prevention* | Vitamin D | Dose expanded |
| | Bisphosphonates, oral (class) | Indication of glucocorticoid-induced osteoporosis added |
| | Alendronic acid (example of class) | Indication of glucocorticoid-induced osteoporosis added |
| - *Secondary prevention of osteoporotic fracture, including patients on long- term corticosteroids* | Bisphosphonates, oral | Recommended as a therapeutic class |
| | Alendronic acid 70 mg, oral | Added as an example of therapeutic class – listed in STG |
| | Alendronic acid 10 mg, oral | Deleted as an example of therapeutic class in the STG, but added to therapeutic interchange database |
| | Risedronic acid 5 mg, oral | Added as a therapeutic alternative |
| | Risedronic acid 35 mg, oral | Added as a therapeutic alternative |
| | Zoledronic acid, IV | Not added as a therapeutic alternative |
| | Ibandronic acid, IV | Not added as a therapeutic alternative |
| **8.14 Paget's disease** | Urgent referral of neurological impairment for IV zoledronic acid | Not added |
| **8.15.3 Diabetes insipidus (posterior hypopituitarism)** | Desmopressin, oral | Directions for use amended |
| | Desmopressin, nasal spray | Directions for use amended |
| | Desmopressin, parenteral | Directions for use amended |
| **8.18.1 Graves' hyperthyroidism** | Beta-blockers, oral | Added as a therapeutic class |
| | Propranolol, oral | Added as a therapeutic alternative |
| | Atenolol, oral | Retained as the example of the beta-blocker group (listed in STG) |
| **Gender dysphoria** | Estradiol, oral | Not added (review for T&Q EML) |
| | Conjugated estrogens, oral | Not added (review for T&Q EML) |
| | Spironolactone, oral | Not added (review for T&Q EML) |
| | Testosterone cypionate, IM | Not added (review for T&Q EML) |
| | Medroxyprogesterone, IM | Not added (review for T&Q EML) |
| **8.18.4 Thyroiditis** | Beta-blockers, oral | Added as a therapeutic class |
| | Propranolol, oral | Added as a therapeutic alternative |
| | Atenolol, oral | Retained as the example of the beta-blocker group (listed in STG) |
| **8.18.5 Thyroid crisis** | Beta-blockers, oral | Added as a therapeutic class |
| | Propranolol, oral | Added as a therapeutic alternative |
| | Atenolol, oral | Retained as the example of the beta-blocker group (listed in STG) |

## 8.2 ADRENAL INSUFFICIENCY (ADDISON DISEASE)

**Investigations**

ACTH depot, IM: *dose retained at "1 mg"*

The 1mg/ml preparation is readily available, whilst the 250 mcg preparation is only available on a named-patient basis with permission from the South African Health Products Regulatory Authority.

**Level of Evidence: III Guidelines**[1]

**During times of severe "stress" i.e. acute illness, surgery, trauma, etc.:**

Hydrocortisone, IV: *dose retained at "100 mg 6 hourly"*

Aligned with the European Society of Endocrinology Guidelines[2], that recommends "*Hydrocortisone 100 mg iv immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day".* The Society acknowledged paucity of RCT evidence investigating corticosteroid dosing in patient with adrenal insufficiency during times of increased cortisol need, and severity and duration of the stressor usually determines the dose. The Guideline recommendation placed a higher value on prevention of adrenal crisis

[1] SAMF, 2016

[2] Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

than on reducing the potential negative effect of short-term overtreatment. The recommendation in the STG is an adaptation of the European Society of Endocrinology Guidelines, adapted for pragmatic purposes.
**Level of Evidence: III Guidelines**

## 8.3 ANDROGEN DEFICIENCY

Testosterone cypionate, IM: *dosing not amended; directions for use amended*
*Dose:* Aligned with MCC registered package insert for management of eunuchoidism. The dose of 100-200 mg every 3-6 weeks is recommended for treatment of oligosperma that is not managed at secondary level of care.
Approved package insert for testosterone cypionate[3] recommends:

- 200 – 400mg injected every 3-4 weeks for eunuchoidism
- 100 – 200mg every 3-6 weeks for oligospermia.

**Level of Evidence: III Package insert, Expert opinion**

*Directions for use:* Guidance provided that testosterone therapy be stopped, if haematocrit exceeds 54%. Meta-analysis[4] (studies of low to medium methodological quality) showed that testosterone treatment was associated with a significant increase in haemoglobin: weighted mean difference (WMD), 0.80 g/dl; 95% CI 0.45 to 1.14; and haematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). No significant effect on mortality, prostate, or cardiovascular outcomes.
**Level of Evidence: I Meta-analysis**

## 8.5 DIABETES MELLITUS

**Diagnosis**
HbA1C: *not added for diagnosing diabetes mellitus*
Refer to the October 2017 evidence summary: Should HbA1C be used as a diagnostic test for diabetes mellitus?

HbA1C for Diagnosising DM_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Evidence is inconclusive regarding the race/ethnic influence on HbA1C. The test has not been validated in the South African population to diagnose diabetes and is more expensive than the current standard finger prick glucose test.
**Level of Evidence: III Human genetic studies, Prevalence study, Guidelines**

Oral glucose tolerance test: *added*
The 2-hour plasma glucose in a 75g oral glucose tolerance test ≥ 11.1 mmol/l was added as an option to diagnose diabetes mellitus, aligned with guidelines.
**Level of Evidence: III Guidelines[5]**

**Monitoring:**
Urine protein monitoring by dipstick: *baseline and annual monitoring added*
*Recent studies* have made it clear that both kidney function (eGFR) and albuminuria are independent risk factors for progression to kidney failure[6]. Both are required to diagnose and monitor diabetic kidney disease. Albuminuria is

[3] Pfizer, MCC registered package insert: Depo-testosterone™, 31 January 2016.
[4] Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. https://www.ncbi.nlm.nih.gov/pubmed/20525906
[5] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[6] Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883.

often detected long before the eGFR drops, thus allowing for earlier CKD diagnosis and intervention[7]. Diabetic kidney disease may classically progress form subclinical disease to the earliest clinical detectable stage, characterized by persistent proteinuria[8].
*PHC 2014 STG* recommends routine screening for microalbuminuria. Despite a Cochrane review[9] suggesting that ACE-inhibitors reduce the risk of new onset moderate and severe albuminuria, PHC STGs and EML[10] recommends screening rather than routine administration of an ACE inhibitor to every diabetic at primary level; as prevalence of diabetics with microalbuminuria is low[11] [12]. The PHC STGs and EML and the current Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines[13] recommends annual screening, except patients already on an ACE Inhibitor in order to minimise wasteful expenditure.
Monitoring for urine protein by dipstick was aligned with the PHC STGs and EML, for consistency and correctness.
**Level of Evidence: III Guidelines**

Serum lipids: *annual monitoring not added*
Despite annual screening of lipids being standard of care as per guidelines[14], the current local public healthcare approach is a "fire and forget" approach, as the "treat to target" approach is too expensive. Intervention of an increased dose of statin following a laboratory result of increased serum lipids is currently not recommended in the STGs.
**Level of Evidence: III Expert opinion**

### 8.5.1 TYPE 2 DIABETES MELLITUS

Glimepiride, oral: *maximum dose added*
Maximum dose of 8 mg per day was added to the text of the STG, aligned with the SAMF 2016; though the approximate equivalent dose of glimepiride to gliclazide is 2:160 mg.
**Level of Evidence: III Guidelines[15]**

Gliclazide, slow release oral: *not added*
Glucagon-like peptide 1 receptor agonist (GLP1 RA), oral: *not added*
Sodium glucose transporter 2(SGLT2) inhibitor, oral: *not added*
Dipeptidyl-peptidase-4 (DPP4) inhibitor, oral: *not added*
Pioglitazone, oral: *not added*

The NEMLC had previously recommended glimepiride or glibenclamide as the sulfonylureas of choice, as gliclazide was considered to be comparable to glimepiride. Gliclazide (both the immediate- and slow release formulations) considered to be expensive. The other oral agents listed above to be considered for review by the Tertiary & Quaternary Committee.

Metformin, oral: *dose amended in renal impairment*
Aligned with the SEMDSA Type 2 Diabetes Guidelines Expert Committee Clinical Practice Guidelines, 2017.
**Level of Evidence: III Guidelines[16]**

[7] Levey AS, Becker C, Inker LA.Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review.JAMA. 2015 Feb 24;313(8):837-46.
[8] McFarlane P. Gilbert RE, MacCallum L, Senior P. Chronic Kidney Disease in Diabetes. Can J Diabetes 37 (2013) S129eS136.
[9] Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2012Dec 12;12:CD004136.
[10] National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/
[11] Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematicreview. World J Diabetes. 2015 Jun 10;6(5):759-73.
[12] MR Davids, N Marais, JC Jacobs. South African Renal Registry. Annual Report2012. South African Renal Society, Cape Town 2014.
[13] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[14] Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care. 2017 Jan;40(Suppl 1):S4-S5.
[15] SAMF, 2016
[16] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

### 8.5.1 TYPE 1 DIABETES MELLITUS

Long-acting insulin analogues: *not added*
External comment was received to consider insulin analogues; for review by the Tertiary & Quaternary Committee at tertiary/quaternary level of care.

Home glucose monitoring: *amended*
Frequency of monitoring for patients on basal/bolus insulin was amended from "at least once daily" to "3-4 times a day" for correctness.
**Level of Evidence: III Expert opinion**

### 8.6.1 HYPOGLYCAEMIA

**In hospital**
Dextrose 50%, IV: *retained*
Glucagon, IM: *deleted*

*Dextrose 50%, IV:* An external comment was received motivating for lower concentrations of dextrose as 50% was reported to cause extravasation. However, there is a paucity of evidence of extravasation injuries associated with 50% dextrose, IV[17]. The current recommendation for administering dextrose 50%, IV for hypoglycaemia was retained; as this was considered appropriate for the clinical setting at secondary level of care, and is aligned with 2017 SEMDSA guidelines[18].
**Level of care: III Guidelines, Expert opinion**

*Glucagon, IM:* A systematic review and meta-analysis by Boido et al (2015)[19] showed that in comparison to IV dextrose, glucagon had frequent reports of being inefficacious; OR 0.53 (95% CI 0.20 to 1.42) favouring the use of dextrose. The authors concluded that a second dose should be administered if no other remedies are available and if the patient does not respond within 15 minutes. Furthermore, if glycogen levels are depleted as might be the case in severe starvation, adrenal insufficiency or alcoholic hypoglycaemia, glucagon might not be effective in raising blood glucose levels.
**Recommendation:** Glucagon, IM deleted from the EML for management of hypoglycaemia at secondary level of care.
*Rationale:* A systematic review and meta-analysis showed that in comparison to IV dextrose, glucagon had frequent reports of being inefficacious; OR 0.53 (95% CI 0.20 to 1.42) favouring the use of dextrose. Dextrose, IV is readily accessible at district hospitals.
**Level of evidence: I Systematic review, Guidelines**

### 8.7.1 DIABETIC NEUROPATHIES

Amitriptyline, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*
Paracetamol, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*
Carbamazepine, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*

### 8.8 DYSLIPIDAEMIA

HMGCoA reductase inhibitors: *indication extended to include CKD and microalbuminuria*

[17] Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. Emerg Med J. 2005 Jul;22(7):512-5.
[18] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[19] Boido A, Ceriani V, Pontiroli AE. Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: a systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. Acta Diabetol. 2015 Apr;52(2):405-12. https://www.ncbi.nlm.nih.gov/pubmed/25323325

*Guidelines:* South African heart association and the lipid and atherosclerosis society of Southern Africa (LASSA) guidelines[20] recommend starting statins in all patients with CKD and type 1 diabetics with microalbuminuria or proteinuria.
*Hou et al[21]:* A systematic review looking at statin therapy in CKD patients (eGFR<60 ml/min/1.73 $m^2$) found that major cardiovascular events were reduced by 23%, including a 22% reduction in coronary events, and 9% reduction in cardiovascular or all-cause death. Although the most benefit is seen in patients with earlier stages of CKD, there was modest benefit in dialysis/non-dialysis stage 5 patients too. A subgroup analysis of 3 trials with >40% diabetics, showed a similar statistically significant benefit of 17% when using statins in CKD.
*Qin et al[22]:* Systematic review and meta-analysis al looking at the effects of statins on renal outcomes in patients with diabetic kidney disease, found that statins have beneficial effects on reducing albuminuria in diabetic kidney disease patients. However, there was no evidence that the same intervention had an effect on overt proteinuria or eGFR outcomes in these patients.
*PHC STGs and EML:* Further aligned with most recent NEMLC approved PHC STGs and EML[23] recommendation.

**Recommendation:** Indication for HMGCoA reductase inhibitors extended to include CKD and microalbuminuria.
*Rationale:* Available evidence suggests that statins are beneficial in reducing major cardiovascular events, coronary events, cardiovascular or all-cause death in patients with CKD. However, statins were shown to reduce albuminuria and not overt proteinuria or eGFR, in diabetic kidney disease patients
**Level of Evidence: I Systematic reviews**

**Alignment with NEMLC-approved PHC STGs and EML**
Recommendations aligned with most recent NEMLC approved PHC STGs and EML, 2018[24] recommendation.
Refer to the PHC Cardiovascular NEMLC report (2016-2018), published on the National Department of Heath website for detailed information (indications, dosing, drug-drug interactions, side-effects, members of therapeutic groups). Available at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc

PHC_Cardiovascular
_NEMLC report_2016

**Myalgia**
The Adult Hospital Level STGs and EML, 2019 recommends that if myalgia develops whilst on a statin, then to reduce the dose to simvastatin 10 mg or equivalent. The Adult Hospital Level Committee recommends that provision be made for 20 mg simvastatin or equivalent and that this be listed on the therapeutic interchange database.

**Drug interaction of statins with amlodipine**
Simvastatin, oral (or equivalent): *dose amended from "10 mg" to "10-20 mg"*

*Background:* An external comment was received about the use of a dose higher than simvastatin 10 mg with concomitant amlodipine.

*Review:* Simvastatin is metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) and is a substrate of CYP3A4. Amlodipine is a weak inhibitor of CYP3A4, with simvastatin being susceptible to the inhibitory effect of amlodipine. Amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin.[25] Concomitant administration of amlodipine with simvastatin could lead to a greater risk of adverse effects such as myopathy and

[20] South African heart association and the lipid and atherosclerosis society of Southern Africa (LASSA). South African dyslipidaemia guideline consensus statement. S Afr Med J 2012;102:177-188.
[21] Hou W,et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013 Jun;34(24):1807-17. https://www.ncbi.nlm.nih.gov/pubmed/23470492
[22] Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2017 Sep;33(6). https://www.ncbi.nlm.nih.gov/pubmed/28477396
[23] Minutes of the NEMLC meetings of 1 February 2018 and 12 April 2018.
[24] Minutes of the NEMLC meetings of 1 February 2018 and 12 April 2018.
[25] Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7.

rhabdomyolysis. A dose of maximum 20 mg simvastatin together with amlodipine 10 mg, has been found to be safe and effective.[26] A dose exceeding 20 mg simvastatin in combination with 10 mg amlodipine is not recommended.
Atorvastatin, a substrate of CYP3A4, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine. The dose of atorvastatin is not to exceed 80 mg with concomitant administration of amlodipine 10 mg.[27]

**Recommendation:** Reduced dose of simvastatin 10 to 20 mg be recommended for patients on concomitant amlodipine.
*Rationale:* Drug-drug interaction of simvastatin with amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin with possible subsequent myopathy and rhabdomyolysis. Pharmacokinetic studies suggests that maximum dose of simvastatin 20 mg is safe when used in combination with amlodipine 10 mg. Atorvastatin, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine and thus, atorvastatin 20 mg is recommended for use with concomitant amlodipine.
**Level of Evidence: III Pharmacokinetic studies, Guidelines**

| Indication/Assessment | Recommendation |
|---|---|
| **Primary prevention of ischaemic events** | Simvastatin, oral: *dose retained as 10 mg* |
| **Secondary prevention of ischaemic events** | Simvastatin, oral: *dose amended from low 10 mg dose to intermediate 40 mg dose* |
| **Secondary prevention of ischaemic events:**<br>**i) Drug-drug interaction with amlodipine** | Simvastatin, oral: *10-20 mg added* |
| **Secondary prevention of ischaemic events:**<br>**ii) Drug-drug interaction with protease inhibitors** | Atorvastatin, oral: *10 mg added* |
| **Secondary prevention of ischaemic events:**<br>**iii) Managing ADRs associated with intermediate dose statins** | e.g. Simvastatin, oral: *10-20 mg added* |
| **Cardiovascular disease risk assessment** | Screening of IHD risk using BMI: *added*<br>Screening of IHD risk using Framingham tables: *retained* |

## 8.9 HYPERCALCAEMIA, INCLUDING PRIMARY HYPERPARATHYROIDISM

Bisphosphonates, IV: *recommended as a therapeutic class and dose adjustment added for renal impairment*
Pamidronic acid, IV: *deleted from STG, as discontinued from market (but retained on therapeutic interchange database)*
Zoledronic acid, IV: *added as an example of therapeutic class – listed in STG*
Ibandronic acid, IV: *added as a therapeutic alternative*
**Background:** Previously, pamidronic acid, IV was recommended for hypercalcaemia, including primary hyperparathyroidism in the Adult Hospital Level STGs and EML, 205 edition. However, this medicine has been discontinued form the South African market. The Adult Hospital Level Committee reviewed the evidence for consideration of bisphosphonates, IV as a therapeutic class in this clinical setting.

Refer to the medicine review, bisphosphonates for hypercalcaemia (September 2017):

Bispohsphonates for Hypercalcaemia_
http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

**Recommendation:** Based on the effectiveness of bisphosphonates therapy for hypercalcaemia and the discontinuation of the pamidronic acid in South Africa, alternative bisphosphonate therapy was required. Zoledronic 4mg, IV and ibandronic 2-4 mg, IV were options that could be considered. Zoledronic acid was the cheapest agent to be listed as the example of class in the STG. The NEMLC recommended the Adult Hospital Level Committee review the evidence

[26] Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8.
[27] SAMF, 2016/2020

for a lower dose of zoledronic acid, possibly to 2 mg. However, no available RCT evidence or guideline recommendations could be sourced for low dose zoledronic acid, IV in this clinical setting. However, dose adjustments are recommended in real impairment and zoledronic acid, IV is contra-indicated when eGFR < 35ml/min.

*Rationale:* Evidence of comparable effectiveness of bisphosphonates (pamidronic acid, zoledronic acid and ibandronic acid).

**Level of Evidence: II Systematic review of low quality RCTs[28] [29], III Guidelines[30] [31]**

Text of the STG was updated to:

- Bisphosphonates, e.g.:
- Zoledronic acid, IV infusion, 4 mg over 15 minutes (specialist initiated).
  - eGFR 35 to 60 ml/min, adjust dose in consultation with specialist.

**Note**: Do not use if eGFR < 35 ml/min.

## 8.10 HYPOCALCAEMIA

**For acute hypocalcaemia with neurological problems**

Calcium gluconate, infusion: *dosing amended*

*Guidelines*[32] recommends administration of calcium in hypocalcaemia where serum calcium <2 mmol/L, as calcium gluconate 10% 20ml in 100ml dextrose 5% over 20 minutes with ECG monitoring as initial management to raise calcium for 1-2 hours, followed with an infusion of 15mg elemental calcium/kg body weight over 4-6 hours (10ml 10% Ca gluconate contains 90mg elemental calcium i.e. 9mg/ml).

The STG was updated as follows:

- Calcium gluconate 10%, infusion, 20 mL in 100 mL dextrose 5% given over 20 minutes, with ECG monitoring.

**AND**

- Calcium gluconate 10%, infusion, 15 mg/kg (= wt [kg] x1.7mL) in 1000 mL sodium chloride 0.9% over 4 hours.

**Level of Evidence: III Guidelines**

## 8.12 OSTEOPOROSIS

**Primary prevention**

Vitamin D: *dose expanded*

Dose expanded to include daily (800 units) and weekly dosing (50 000 units), as suggested by SAMF, 2016.

**Level of Evidence: III Guidelines[33]**

**Glucocorticosteroid-induced osteoporosis (GIOP)**

Bisphosphonates, oral (class): *indication of glucocorticoid-induced osteoporosis added*

Alendronic acid (example of class): *indication of glucocorticoid-induced osteoporosis added*

*Background:* During the final clinical editing process of the Adult Hospital Level STGs and EML, 2019 edition, guidance for glucocorticosteroid-induced osteoporosis (GIOP) was included in section 13.6 Systemic lupus erythematosus (SLE) as below (accepted by NEMLC electronically):

[28] Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, Broadley K. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess. 2004;8(4):1-176. https://www.ncbi.nlm.nih.gov/pubmed/14960258

[29] Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001 Jan 15;19(2):558-67. https://www.ncbi.nlm.nih.gov/pubmed/11208851

[30] SAMF, 2016

[31] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[32] Tohme JF, Bilezikian JP. Diagnosis and treatment of hypocalcaemic emergencies. The Endocrinologist. 1996; 10-18.

[33] SAMF, 2016

Patients requiring corticosteroids for >3 months (long-term) should be managed for secondary prevention of osteoporotic fractures. See section 8.12: Osteoporosis.

**Level of Evidence: I Systematic review and meta-analysis**

**Query:** However, section 8.12 does not provide sufficient guidance for GIOP, and this has created confusion amongst end-users of this guideline. Query had been received from George, Western Cape.

*Glucocorticoid-induced osteoporosis:* Corticosteroids (immunosuppressants) are widely used in inflammatory conditions, but bone-loss and GIOP is a serious adverse drug reaction associated with chronic corticosteroids[2].

*Evidence:* Cochrane review[34] of 12 RCTs (n=1343) showed that amongst adults taking chronic corticosteroids (mean steroid dose ≥5.0 mg/day), 2% fewer (95% CI 5% fewer to 1% more) sustained incident vertebral fractures with bisphosphonates vs. no bisphosphonates, followed up over a period of 24 months (high-certainty evidence); RR 0.57 (95% CI 0.35 to 0.91), $I^2$=0%; NNTB 31 (95%CI 21 to 145).

Low-certainty evidence suggested that bisphosphonates may make little or no difference in preventing non-vertebral fractures; RR 0.79 (95% CI 0.47 to 1.33), $I^2$=0%. Whilst moderate-certainty evidence showed that bisphosphonates are beneficial in preventing and treating corticosteroid-induced bone loss at both the lumbar spine and femoral neck; Mean difference 3.5 (95% CI 2.9 to 4.1), $I^2$=69.93%.

Low-certainty evidence showed that bisphosphonates may be associated with a low number serious adverse events or withdrawals due to adverse events; however, the authors cautioned about the possible risk of bias. Rare serious adverse events associated with bisphosphonates includes osteonecrosis of the jaw and atypical femur fractures[35].

Authors concluded that the use of bisphosphonates reduces the risk of vertebral fractures and the prevention and treatment of steroid-induced bone loss. The main limitation of this meta-analysis was the heterogeneity between RCTs (possibly due to different patient characteristics, underlying inflammatory conditions, steroid doses, and prevalent fractures and reported outcomes).

*Study participants in the Cochrane review:* Adults (>18 years) with underlying inflammatory disorders, initiating treatment or currently being treated with systemic corticosteroids, and who had not received bisphosphonates in the six months prior to the start of the study. In GIOP literature, the concept of rapid bone loss within the first three to six months of corticosteroid use is described.[36] [37]

*Steroid dose and duration in the Cochrane review:* RCTs included in the review had a mean corticosteroid dose of ≥5 mg/day (e.g. prednisone, oral), and participants were on therapy throughout the duration of the study. Study periods varied from 12 to 48 months. RCTs of patients on transplant-associated steroid use were excluded from the review.

*Concomitant medicine in the Cochrane review:* RCTs evaluated bisphosphonates with or without calcium and/or vitamin D as the active treatment arm; whilst the comparators included calcium and/or vitamin D or placebo.

Guidance for primary prevention of osteoporosis was expanded in the STG to adequately describe guidance for GIOP, as follows:

**Primary prevention:**
For glucorticoid-induced osteoporosis, i.e. patient on long-term (>3 months) corticosteroids at doses ≥5 mg/day
- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

**Secondary prevention of osteoporotic fracture~~, including patients on long- term corticosteroids:~~**
In severe osteoporosis, i.e. patients who have a T-score of –2.5 (severe osteoporosis) plus an osteoporotic fracture.
- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

[34] Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev*. 2016;10(10):CD001347. https://pubmed.ncbi.nlm.nih.gov/27706804/
[35] SAMF, 2016
[36] Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319-1328. https://pubmed.ncbi.nlm.nih.gov/17566815/
[37] van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002;13(10):777-787. https://pubmed.ncbi.nlm.nih.gov/12378366/

Supplement bisphosphonate therapy with:

- Calcium, elemental, oral, 1 000mg daily.

**AND**

- Vitamin D (Calciferol), oral, 800 units daily.

**Level of Evidence: I Meta-analysis**

**Secondary prevention of osteoporotic fracture, including patients on long-term corticosteroids**

Bisphosphonates, oral: *recommended as a therapeutic class*
Alendronic acid 70 mg, oral (weekly dose): *added as an example of therapeutic class – listed in STG*
Alendronic acid 10 mg, oral (daily dose): *deleted as an example of therapeutic class in the STG, but added to therapeutic interchange database*
Risedronic acid 5 mg, oral (daily dose): *added as a therapeutic alternative*
Risedronic acid 35 mg, oral (weekly dose): *added as a therapeutic alternative*
Zoledronic acid, IV: *not added as a therapeutic alternative*
Ibandronic acid, IV: *not added as a therapeutic alternative*

Refer to the medicine review, bisphosphonates for osteoporosis (October 2017):

Bisphosphonates for Osteoporosis_Ac

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

**Recommendation:** Based on the evidence review on the effectiveness of bisphosphonates therapy for preventing fragility fractures, oral bisphosphonates were recommended as a therapeutic class on the secondary level EML (i.e. alendronic acid 70 mg, risedronic acid 35 mg, alendronic acid 10 mg and risedronic acid 5 mg - the least expensive agent, alendronic acid 10 mg daily is preferred, but the other oral agents may be considered where there are supply chain issues).

*Rationale:* Clinically all bisphosphonates reduced the risk of vertebral fractures compared with no treatment. No bisphosphonate was found to be superior to any other at preventing fractures. All treatments were associated with beneficial effects relative to placebo.
Pairwise comparisons between treatments indicated that no active treatment was statistically significantly more effective than any other active treatment for fracture outcomes. For vertebral fractures and percentage change in femoral neck BMD, the greatest effect was for zoledronic acid, although in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects. There was no evidence to suggest different treatment effects according to age or sex. Oral bisphosphonates have similar rates of gastrointestinal toxicity when compared with placebo; whilst Intravenous bisphosphonates, especially zoledronic acid, are more likely to predispose patients to osteonecrosis of the jaw.
The de novo economic model from the systematic review suggests that the cost-effectiveness of IV bisphosphonates (ibandronic acid and zoledronic acid) is less favourable than for oral bisphosphonates with a negative incremental net benefit compared to no treatment; estimated for both IV bisphosphonates across all 10 risk categories for both FRAX and QFracture.
**Level of Evidence: I Health Technology Assessment**[38]

## 8.14 PAGET'S DISEASE

**Referral**

Urgent referral of neurological complications: *not added*
External comment to refer neurological complications for IV zoledronic acid was not considered, as there is a paucity of RCT evidence that zoledronic acid, IV prevents/improves long-term neurological impairment. Despite, limited evidence

[38] Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess 2016;20(78). https://www.ncbi.nlm.nih.gov/pubmed/27801641

showing that zoledronic IV improves bone pain and quality of life; all patients are referred for management at tertiary level of care.

### 8.15.3 DIABETES INSIPIDUS (POSTERIOR HYPOPITUITARISM)

Desmopressin, oral: *directions for use amended*
Desmopressin, nasal spray: *directions for use amended*
Desmopressin, parenteral: *directions for use amended*

Guidance for the management of diabetes insipidus with desmopressin was updated as follows, aligned with expert opinion[39] [40]:

Postoperative or acutely ill patients:

- Desmopressin, IV/SC, 2–4 mcg daily, either as a single dose or in 2 divided doses.

**OR**

Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.

**OR**

Desmopressin, oral, 0.05 mg, 8–12 hourly.

- Optimal dose: 0.1–0.8 mg daily.
- Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

If patient has a normal thirst mechanism, and does not receive IV fluids for other purposes:

» oral, intranasal, or IV/SC dosing can be used; and
» keep urine osmolality at 450–600 mOsm/kg.

If patient requires IV fluids and/or is unable to regulate total fluid intake by thirst mechanism:

» IV dosing is preferred; and
» continually adjust the level of antidiuresis to maintain hydration and plasma sodium within the normal.

Replacement therapy:

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.
  - Adjust morning and evening doses separately for appropriate diurnal rhythm of water turnover.

**OR**

Desmopressin, oral, 0.05 mg, either as a single dose or in 2–3 divided doses.

- Optimal dose: 0.1–0.8 mg daily.
- Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

**Level of Evidence: III Expert opinion**

### 8.18.1 GRAVES' HYPERTHYROIDISM

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group (listed in STG)*

Previously, it was recommended that propranolol not be recommended for management of Graves' hyperthyroidism due to possible concerns of associated heart failure[41] and the advantage of daily dosing of atenolol as opposed to 8 hourly dosing of propranolol. However, this is currently standard of care and extensively used in clinical practice.
**Level of Evidence: III Pharmacokinetic studies, Expert opinion**

[39] Oiso Y, Robertson GL, Nørgaard JP, and Juul KV. Treatment of Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab 98: 3958–3967, 2013.
[40] British National Formulary, September 2017-March 2018 edition.
[41] SAMF, 2016

| Beta-blocker, oral therapeutic group for hyperthyroidism | | | |
|---|---|---|---|
| *Medicine* | *Daily dose* | *Level of evidence* | *Price of daily dose*[42] |
| Atenolol, oral | 100 mg daily | **Level of evidence: III**<br>**Pharmacokinetic studies**[43] [44]**,**<br>**Expert opinion**[45] | R 0.15 |
| Propranolol, oral | 40-80 mg 8 hourly | | R 0.22 to R 0.44 |

## GENDER DYSPHORIA

Estradiol, oral: *not added*
Conjugated estrogens, oral: *not added*
Spironolactone, oral: *not added*
Testosterone cypionate, IM: *not added*
Medroxyprogesterone, IM: *not added*

Motivation initially submitted to PHC Committee, and deliberations were made regarding management of this condition at secondary level of care or rather specialised treatment at tertiary level of care with down-referral.
The Adult Hospital Level Committee recognised the importance of managing gender dysphoria but was of the opinion that expertise is required within a specialised unit.
**Recommendation:** The motivation be reviewed by the Tertiary and Quaternary Committee for consideration.

## 8.18.4 THYROIDITIS

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group*
Aligned with section 8.18.1: Graves' hyperthyroidism.

## 8.18.5 THYROID CRISIS

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group*
Aligned with section 8.18.1: Graves' hyperthyroidism.

*Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)*
- ***Note**: Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[42] Contract circular RT289-2019: Average weighted price of 40mg propranolol = R0.222; Atenolol 100mg tabs, 28 = R4.15.
[43] Perrild H, Hansen JM, Skovsted L, Christensen LK. Different effects of propranolol, alprenolol, sotalol, atenolol and metoprolol on serum T3 and serum rT3 in hyperthyroidism. Clin Endocrinol (Oxf). 1983 Feb;18(2):139-42. https://www.ncbi.nlm.nih.gov/pubmed/6133659
[44] Wilkins MR, Franklyn JA, Woods KL, Kendall MJ. Effect of propranolol on thyroid homeostasis of healthy volunteers. Postgrad Med J. 1985 May;61(715):391-4. https://www.ncbi.nlm.nih.gov/pubmed/3927277
[45] Geffner DL, Hershman JM. Beta-adrenergic blockade for the treatment of hyperthyroidism. Am J Med. 1992 Jul;93(1):61-8. https://www.ncbi.nlm.nih.gov/pubmed/1352658