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The Sri Lanka Prescriber

The Sri Lanka Prescriber is the only national, independent drugs and therapeutics bulletin in the country. Published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo, in collaboration with the State Pharmaceutical Corporation, it has served as a source of unbiased, evidence-based information for over several decades.

The Sri Lanka Prescriber evolved from the pocket size bulletins published by the Department of Pharmacology, Formulary Notes, which began publishing in 1966, continued as 'The Prescriber' from 1973. The Sri Lanka Prescriber started publication in the current format in 1993, which is also a continuation of the two previous bulletins. The Sri Lanka Prescriber continues with an updated scope and an editorial Board from 2025.

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Dedicated to supporting informed prescribing decisions, the Sri Lanka Prescriber offers content relevant to clinicians, pharmacists, academics, and students in medicine and allied health fields.

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- Independent drug reviews and cost-effectiveness evaluations
- Regulatory updates from the National Medicines Regulatory Authority (NMRA)
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Protocol-based Pharmacological Management of Hypertension

Background

Hypertension is the most important single risk factor for cardiovascular diseases [1-3]. One in three adults worldwide has hypertension [4]. Despite having enough guidelines, blood pressure control (BP) worldwide is suboptimal. According to the World Health Organisation, approximately 1 in 5 adults with hypertension have BP under control [4]. Poor implementation of guidelines has been identified as a significant reason behind this [4].

Therefore, the Directorate of Noncommunicable Diseases, Ministry of Health, Sri Lanka, in collaboration with the World Health Organisation (WHO), has initiated a project to strengthen BP control in Sri Lanka by expanding the Resolve to Save Lives project. This project aims to improve the coverage for hypertension in Sri Lanka to 50% by 2025 [5]. The project includes protocol-based BP management using the "Simple protocol" adopted for Sri Lanka based on the Resolve to Save Lives and the World Hypertension League (WHL) protocol [6]. The "Simple Protocol for BP management" essentially gives the stepwise approach for pharmacological management of hypertension and is published in the latest National Guideline for the Management of Hypertension for Primary Healthcare Providers of Sri Lanka (Figure 1) [7].

"Simple" Protocol for pharmacological management of hypertension

The "Simple" Protocol for the pharmacological management of hypertension is given in Figure 1. Hypertension is defined as BP of 140/90 mmHg or above. Hypertension is categorised into 2 grades as;

Grade 1 – BP 140-159/90-99 mmHg and

Grade 2 – BP ≥ 160/100 mmHg

All patients except those frail, above 80 years or with Grade 1 hypertension and at low cardiovascular risk are recommended to be started on Algorithm 1 with low-dose dual antihypertensive therapy.

Algorithm 1

- Step 1: losartan 50 mg Once Daily (OD) + amlodipine 5 mg OD
- Step 2: losartan 100mg OD + amlodipine 10 mg OD
- Step 3: losartan 100mg OD + amlodipine 10 mg OD + hydrochlorothiazide (HCT) 12.5 mg OD
- Step 4: losartan 100mg OD + amlodipine 10 mg OD + hydrochlorothiazide (HCT) 25 mg OD
- Step 5: Refer the patient to a specialist if BP is still not controlled on step 4 (Resistant hypertension)

The rationale behind initiation with low-dose dual antihypertensive therapy is to achieve BP goals in a short period with minimal side effects. This regimen is associated with fewer side effects as low doses of drugs are used. The regimen is more efficacious as two classes of drugs acting in different mechanisms give synergistic effects in BP control. Initiation of two drugs at the beginning further allows for the reduction of physician inertia in BP control, as most patients eventually require more than one blood pressure-lowering medication.

Patients who are frail, above 80 years or with Grade 1 hypertension and at low cardiovascular risk are recommended to be started on algorithm 2 with low-dose single antihypertensive therapy.

Algorithm 2

- Step 1: amlodipine 5 mg OD
- Step 2: amlodipine 10 mg OD
- Step 3: amlodipine 10 mg OD + losartan 50mg OD
- Step 4: amlodipine 10 mg OD + losartan 100mg OD
- Step 5: amlodipine 10 mg OD + losartan 100mg OD + hydrochlorothiazide (HCT) 12.5 mg OD
- Step 6: amlodipine 10 mg OD + losartan 100mg OD + hydrochlorothiazide (HCT) 25 mg OD
- Step 7: Refer the patient to a specialist if blood pressure is still not controlled on step 6 (Resistant hypertension)

Follow-up

BP is recommended to be monitored every 4-6 weeks. Antihypertensives are recommended to be titrated according to the protocol until the BP goal is achieved. Once the BP goal is achieved, it is recommended that patients be followed up every 3-6 months.

The WHO treatment target is to reduce BP to <140/90mmHg. However, less stringent BP targets are accepted for those who cannot tolerate such low blood pressures.

Antihypertensive medications

Medications recommended in the protocol are only examples, and they can be replaced with alternative medications according to availability and affordability. Any combination of two first-line antihypertensive medications out of the three main antihypertensive medication classes: renin-angiotensin system (RAS) blockers, calcium channel blockers (CCB), or diuretics can be used at the initiation of treatment. It is important to note that RAS blockers are contraindicated in pregnancy.

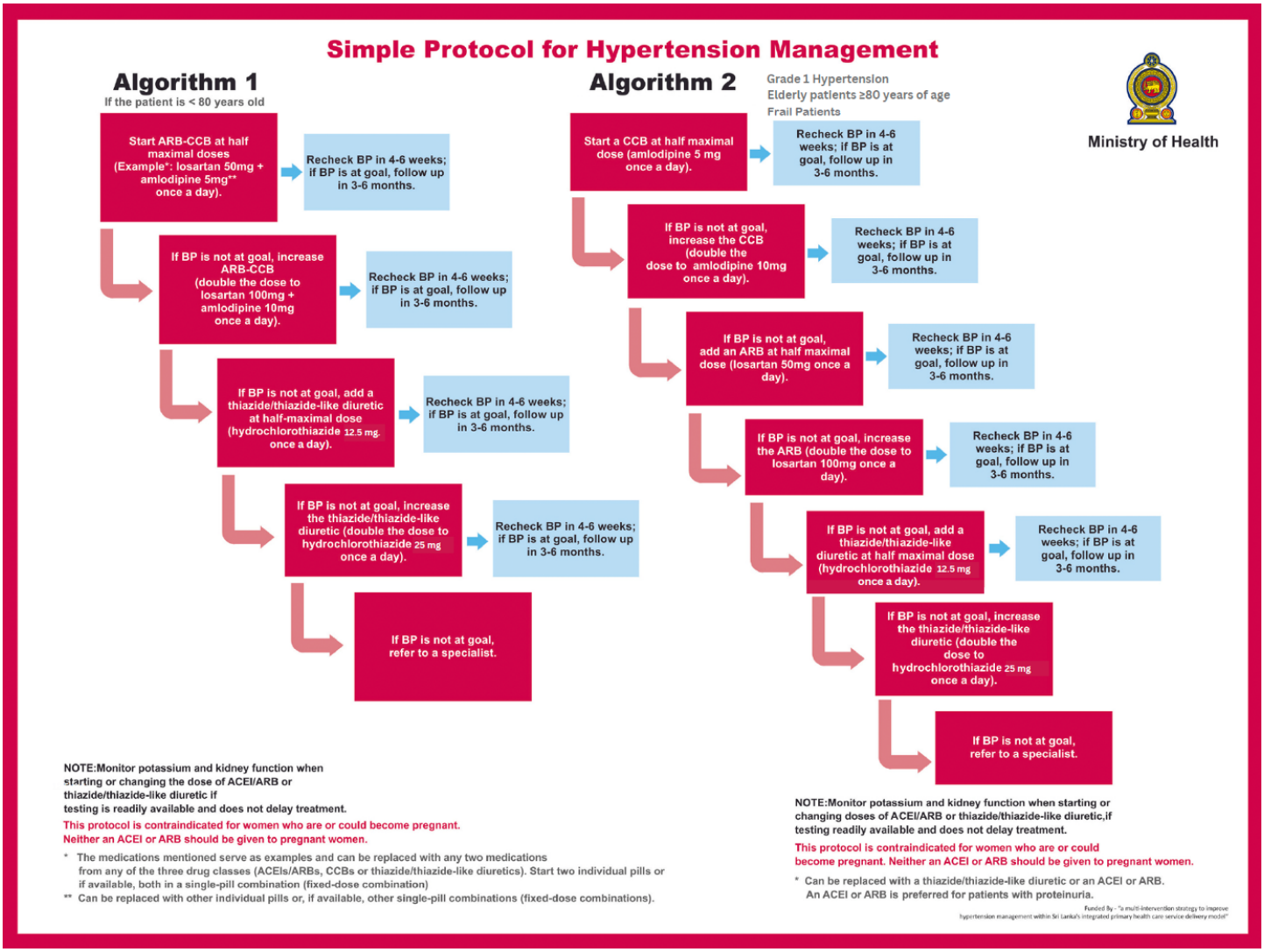

Figure 1: "Simple" protocol for the pharmacological management of hypertension

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Conflict of interest

None declared

Management of dyslipidaemia

Introduction

Dyslipidaemia is an abnormal amount of lipids (fats) in the blood. It typically involves elevated cholesterol levels, triglycerides, or both, or a low level of high-density lipoprotein (HDL) cholesterol. High lipid levels, caused by genetic factors or lifestyle choices, can contribute to the development of atherosclerosis and other cardiovascular issues. It may be related to other diseases (secondary dyslipidaemia) or to the interaction between genetic predisposition and environmental factors. Diagnosis relies on lipid profile tests, with recommended target levels for optimal cardiovascular (CV) health.

All current guidelines on the prevention of Atherosclerotic cardiovascular disease (ASCVD) in clinical practice recommend estimation of total CVD risk. Prevention of ASCVD in a given person relates to total CV risk: the higher the risk, the more intense the action [1] (Table 1).

More recently, in an attempt to produce a single scoring system that can be used globally, World Health Organization (WHO) risk charts were published to permit risk estimation in 21 global regions (Figure 1).

This guideline uses the World Health Organization/ International Society of Hypertension (WH0/ISH) risk prediction chart for SEARO B, WHO epidemiological sub-region based on country-specific cohort data [2]. Treatment strategies work to mitigate risks by targeting specific lipid abnormalities, emphasising lifestyle modifications, and considering comorbidities to individualise care. Given the multifaceted nature of dyslipidaemia management, a multidisciplinary approach is essential for comprehensive patient care. The evidence showing that reducing TC and LDL-C can prevent CVD is strong and compelling, based on results from multiple randomised controlled trials (RCTs).

The recommendations in this section are adoptions from the lipid guidelines for Sri Lanka, which were based on the ACC/AHA guidelines, the *American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines 2018*, ESC 2019, and NICE.

Health professionals are encouraged to adhere to these National Guidelines in implementing preventive, diagnostic, or therapeutic medical strategies. However, these National Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in managing individual patients [3].

Lifestyle modification

Lifestyle modifications play a crucial role in combating dyslipidaemia and reducing the risk of ASCVD. Maintaining a healthy body weight is essential, as weight reduction has been shown to improve lipid profiles. To achieve this, a combination of dietary changes and physical activity is recommended. Decreasing the consumption of energy-dense foods and creating a daily caloric deficit of 300–500 kcal are effective strategies for weight management. This approach should be paired with regular exercise to enhance energy expenditure and promote sustainable weight loss, ultimately contributing to better cardiovascular health [4,5].

Physical activity is equally significant in achieving a favourable lipid profile and overall health benefits. Adults should aim for at least 150–300 minutes of moderate-intensity aerobic exercise or 75–150 minutes of vigorous-intensity aerobic activity weekly. Additionally, incorporating muscle-strengthening exercises targeting all major muscle groups two or more days per week provides extra health advantages [6,7]. For those who are currently inactive, even small amounts of physical activity can be beneficial; gradually increasing the duration, intensity, and frequency over time is encouraged. This comprehensive approach to lifestyle modification not only aids in managing dyslipidaemia but also supports overall well-being and long-term health.

A balanced dietary approach is critical for managing dyslipidaemia and preventing ASCVD. Limiting total fat intake to 30% or less of daily energy and strictly avoiding trans fats are key preventive measures. Carbohydrates should contribute 50–60% of daily energy intake, avoiding excessive amounts to prevent adverse effects on triglycerides (TG) and HDL-C. Including soluble dietary fiber—found in legumes, fruits, vegetables, and whole grains like oats and

barley—can help lower LDL-C levels while substituting saturated fats effectively. This strategy ensures optimal lipid management and promotes cardiovascular health [8].

Research indicates a dose-response relationship between alcohol consumption and blood lipids, particularly highlighting an inverse correlation with HDL-C and excessive alcohol intake (above 30 g/day) may lead to increased levels of triglycerides (TG) and total cholesterol. Smoking cessation and stress management should be promoted [9,10].

Figure 1: World Health Organization/International Society of Hypertension risk charts

Table 01: Risk levels

Very high risk - Documented ASVD - Clinical - Past ACS, Stable angina, PCI, CABG, CVA, TIA, PVD - Imaging - Major plaques on CA, CTCA showing DVD with>50% stenosis, Carotid US, DM with target organ damage or 3 major risk factors: - Early onset of T1DM of long duration (>20 years) - Severe CKD (eGFR <30mL/min/1.73m2) - FH with ASCVD or 1 major risk factor. - Risk score >30%
High risk - Markedly elevated single risk factors TC >310 mg/dL), LDL-C >190 mg/dL, - BP ≥180/110 mmHg. - Patients with FH without major risk factors. - Moderate CKD (eGFR 30-59 mL/min/1.73 m2) - Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor - Risk score 20-30%
Moderate risk - Young patients T1DM <35 years; T2DM <50 years, DM duration <10 years, without other risk factors. - Risk score 10 -20 %
Low risk - Risk score < 10%

ACS - Acute Coronary Syndrome; ASCVD - Atherosclerotic Cardiovascular Disease; BP - Blood Pressure; CABG - Coronary Artery Bypass Grafting; CA - Coronary Angiography; CKD - Chronic Kidney Disease; CT CA - Computed Tomography Coronary Angiography; CVA - Cerebrovascular Accident; DM - Diabetes Mellitus; DVD - Double Vessel Disease; eGFR - Estimated Glomerular Filtration Rate; FH - Familial Hypercholesterolemia; LDL-C - Low-Density Lipoprotein Cholesterol; PCI - Percutaneous Coronary Intervention; PVD - Peripheral Vascular Disease; TC - Total Cholesterol; TIA - Transient Ischemic Attack; T1DM - Type 1 Diabetes Mellitus; T2DM - Type 2 Diabetes Mellitus

Table 02: Primary and Secondary Prevention Goals

Primary Prevention Goals	
Very High risk (ASCVD risk >30%)	LDL<55mg/dL(<1.4mmol/L)
High risk (ASCVD risk>20%-30%)	LDL<70mg/dL(<1.8 mmol/L)
Moderate risk	LDL<100mg/dL(2.6 mmol/L)
Low risk	LDL<116mg/dL(3 mmol/L)
Type 1 DM Age>40 years or Diabetes>10 years Have established nephropathy have other CVD risk factors	LDL<70mg/dL(<1.8mmol/L)
Type 2DM CVD risk>10%	LDL<70mg/dL(<1.8mmol/L)
Secondary Prevention Goals	
Established CVD	LDL<55mg/dL<(1.4mmol/L)
CVD with second event within 2years	LDL<40mg/dL(1mmol/L)

ASCVD – Atherosclerotic Cardiovascular Disease; CVD – Cardiovascular Disease; DM – Diabetes Mellitus; LDL – Low-Density Lipoprotein; T1DM – Type 1 Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus

Pharmacological management

To effectively manage cardiovascular risk, it is essential to evaluate the individual's total CV risk (Figure 1), determine treatment goals based on the current risk, involve the patient in shared decision-making on CV risk management, select an appropriate statin regimen, and, when necessary, incorporate additional treatments to achieve targeted outcomes.

To achieve treatment goals for specific levels of risk, it is recommended to prescribe a high-intensity statin such as atorvastatin or rosuvastatin up to the highest tolerated dose, with combination therapy using ezetimibe if goals are not met. In cases where statin and ezetimibe fail to achieve the target, a PCSK9 inhibitor may be added. Patients unable to tolerate statins at any dose should consider ezetimibe alone, and if necessary, bile acid sequestrants may also be used.

Statin treatment is recommended as the first-line therapy to reduce CVD risk in high-risk individuals with hypertriglyceridemia, with the addition of n-3 fatty acid in patients who have TG levels between 135–499 mg/dL (1.5–5.6 mmol/L) despite statin therapy, and in those at LDL-C goal but with TG levels >200 mg/dL (>2.3 mmol/L), fenofibrate may be considered in combination with statins.

Statin therapy

The choice to begin statin therapy should be made after a thorough discussion between the healthcare provider and the individual, taking into account the advantages and risks of treatment. This decision should also consider factors such as the potential impact of lifestyle changes, the patient's preferences, existing health conditions, concurrent medications, overall frailty, and expected lifespan.

Before starting statin therapy, it is essential to perform baseline blood tests, conduct a clinical assessment, and address comorbidities or secondary causes of dyslipidaemia. Factors such as smoking status, alcohol consumption, blood pressure, body mass index (BMI) or other measures of obesity, fasting blood sugar (FBS) or HbA1c, renal function, estimated glomerular filtration rate, alanine aminotransferase (ALT), and thyroid-stimulating hormone (TSH) should all be evaluated as part of this process.

Additionally, if the patient reports muscle-related symptoms, measure creatinine kinase (CPK) levels. Statin therapy should not be initiated if CPK levels repeatedly exceed five times the upper limit. However, if CPK levels are elevated but remain below this threshold, statin treatment can be started at a lower dose. Similarly, baseline ALT levels should be assessed, but statin therapy need not be excluded in patients with mildly elevated liver transaminase levels that are less than three times the upper limit of normal.

Current evidence from meta-analyses indicates that the clinical benefit of statin therapy is primarily a class effect driven by the degree of absolute LDL-C reduction; hence, the choice of statin should align with the patient's treatment goals. When prescribing statins, it is recommended to opt for high-intensity, cost-effective options. Statins are contraindicated during pregnancy, and patients should be advised to discontinue statins if pregnancy is possible, stop statins three months before conception when planning pregnancy, and avoid restarting statins until breastfeeding is completed.

Table 03: Grouping of statins [1]

Statin	Low-Intensity Dosage (LDL-C Reduction <30%)	Moderate-Intensity Dosage (LDL-C Reduction 30% to <50%)	High-Intensity Dosage (LDL-C Reduction ≥50%)
Simvastatin	10 mg	20 to 40 mg	NA
Atorvastatin	NA	10 to 20 mg	40-80 mg
Rosuvastatin	NA	5 to 10 mg	20 to 40 mg

NA - Not applicable

Primary prevention

Primary prevention involves assessing cardiovascular risk using WHO/ISH SEAR B charts, excluding secondary causes, and offering lifestyle advice. Atorvastatin 20 mg is recommended for individuals with LDL-C levels of 190 mg/dL or higher, those aged 40-75 with type II diabetes or a WHO/ISH CVD risk ≥ 20%, and select cases like type I diabetes patients with additional risk factors or chronic kidney disease. For people 85 or older, atorvastatin may reduce non-fatal myocardial infarction risks, but patient-specific considerations are important. Ezetimibe is an alternative for those contraindicated for statins.

Secondary prevention

Sri Lankans with a history of ASCVD and no CKD are recommended to start atorvastatin 40 mg nocte, though Western guidelines suggest 80 mg. In CKD patients, atorvastatin 20 mg nocte is advised, with dose adjustments if a greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is at least 30 ml/min/1.73m². If eGFR is below 30 ml/min/1.73m², consult a renal specialist regarding higher doses. The guidance does not cover individuals on renal replacement therapy. Ezetimibe monotherapy is recommended when statins are contraindicated.

Scenario 1

A 56-year-old man presented to the medical clinic with a minor stroke, which was conservatively managed a month ago. He is a known hypertensive and was treated for ST-elevating myocardial infarction six months ago. He was on enalapril 5 mg bd, aspirin 75 mg nocte and atorvastatin 40 mg nocte.

His examination findings were normal, with blood pressure of 130/80 mmHg and PR of 82 bpm.

Lipid profile

Total cholesterol	195	mg/dL
Triglyceride	147	mg/dL
HDL	51	mg/dL
LDL	114	mg/dL
VLDL	29	mg/dL
Cholesterol/HDL ratio	3.8	
Non-HDL Cholesterol	144	mg/dL

In this patient having CVD with second event within 2 years his target LDL level Is < 40 mg/dL

Two options are appropriate for his management

Option 01 - Double the atorvastatin dose (40 mg)

Option 02 - Add ezetimibe 10 mg

Scenario 02

A 58-year-old woman presented to the medical clinic with a routine check-up cholesterol report. She has no significant past medical history and is a smoker. Her examination showed blood pressure 160/90 mmHg, PR 80 bpm.

Lipid profile

Total cholesterol	315	mg/dL
Triglyceride	115	mg/dL
HDL	48	mg/dL
LDL	244	mg/dL
VLDL	23	mg/dL
Cholesterol/HDL ratio	7	
Non-HDL Cholesterol	144	mg/dL

In management, her cardiovascular risk needs to be assessed according to the WHO/ISH chart

Her age is 58, she is a smoker and has a blood pressure of 160 mmHg and total cholesterol of 315 mg/dL (8.14 mmol/L), which would give her a 10-year risk of 10-20% (orange 14)

For management lifestyle modification and starting statins either atorvastatin 40 mg or rosuvastatin 20 mg would be indicated.

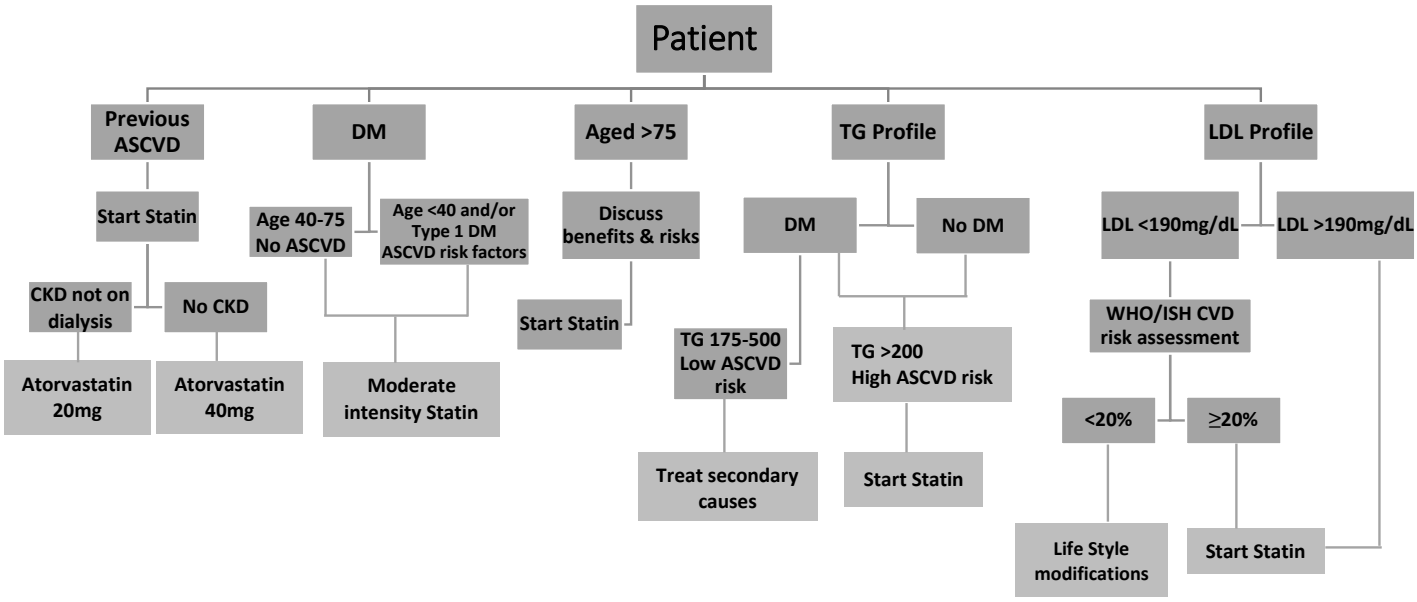

Figure 02: Algorithm, management of dyslipidaemia (ASCVD – Atherosclerotic cardiovascular disease, CKD – Chronic kidney disease; DM –Diabetes mellitus; LDL – Low density lipoprotein; TG – Triglycerides)

Adverse Effects of Statin Therapy

Myopathy, often linked to interactions with concomitant medications, is the most significant adverse effect of statins. The most severe form, rhabdomyolysis, involves intense muscular pain, muscle necrosis, and myoglobinuria, which can result in renal failure or even death, with CPK levels elevated to at least 10 times the upper limit of normal.

Clinically relevant ALT elevation is typically defined as an increase to three times the upper limit of normal on two separate occasions. Mild ALT elevations, occurring in 0.5–2.0% of patients, are not linked to actual hepatotoxicity or impaired liver function.

Since progression to liver failure is extremely rare, routine ALT monitoring during statin therapy is no longer advised [1, 2].

Drug interactions

The involvement of the Cytochrome P-450 (CYP) system in metabolism is a key factor here. Among currently available statins, rosuvastatin and pitavastatin stand out as exceptions, as they do not undergo significant hepatic metabolism via CYPs. Combining statins with gemfibrozil significantly raises the risk of myopathy. However, the risk of myopathy is notably low when statins are combined with other fibrates such as fenofibrate, bezafibrate, or ciprofibrate [1-3].

Statin intolerance

For individuals intolerant to high-intensity statins, it is recommended to use the maximum tolerated dose, as statins at any level lower cardiovascular disease risk. Strategies include stopping the statin temporarily and retrying after symptoms resolve, reducing the dose within the same intensity group, or switching to a lower-intensity statin.

Follow-up and monitoring

Do not routinely measure creatinine kinase in asymptomatic individuals and monitor liver transaminase enzymes at baseline, 3 months, and 12 months. Statins should not be stopped due to increased blood glucose. A lipid profile should be repeated 3 months after starting or adjusting the dose. Annual reviews should address medication adherence, lifestyle changes, and other CVD risk factors, with cholesterol levels assessed using fasting or non-fasting tests. If a greater than 40% reduction in non-HDL cholesterol is not achieved, adherence and timing of doses should be discussed, diet and lifestyle measures optimised, and dose adjustments should be considered for higher-risk individuals on lower doses of atorvastatin.

Intolerance of insufficient response to statins

Ezetimibe monotherapy is an option for those unable to tolerate statins. Additionally, ezetimibe can be co-administered with initial statin therapy if serum total or LDL cholesterol levels remain uncontrolled after appropriate dose adjustments, if dose titration is limited by statin intolerance, or if switching to an alternative statin is considered.

Promoting heart-healthy lifestyle choices throughout life is essential for everyone. Patients with clinical ASCVD should aim to lower LDL-C levels through high-intensity statin therapy or the maximum tolerated dose. For individuals with LDL below 190 mg/dL, lipid-lowering treatments should focus on ASCVD risk rather than solely on cholesterol levels. Statins remain the primary treatment option for high-risk individuals with hypertriglyceridemia, and therapy should be maintained without reduction after achieving targets. Lipid measurements should be assessed 4 to 12 weeks after initiating or adjusting statin therapy and subsequently monitored every 3 to 12 months as needed.

Conclusion

Screening for non-communicable diseases, including hyperlipidaemia, should be actively encouraged at all levels, with healthy lifestyle centers in government hospitals playing a key role. Identifying risk categories for active screening is crucial, while large-scale screening should be focused on carefully chosen groups. All current guidelines on the prevention of Atherosclerotic cardiovascular disease (ASCVD) in clinical practice recommend estimation of total CVD risk. To achieve treatment goals for specific levels of risk, it is recommended to prescribe a high-intensity statin up to the highest tolerated dose, with combination therapy using ezetimibe if goals are not met.

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Conflict of interest

None Declared.

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MCQs - Management of Dyslipidaemia

1. Which statements regarding the pharmacological treatment of high cholesterol are correct?
   A. Statins reduce LDL cholesterol by inhibiting HMG-CoA reductase
   B. Ezetimibe acts by increasing the excretion of bile acids
   C. PCSK9 inhibitors are monoclonal antibodies that increase LDL receptor recycling
   D. Fibrates are primarily used to reduce HDL cholesterol
   E. Niacin increase HDL level

2. Which lifestyle modifications are effective in lowering cholesterol levels?
   A. Diet high in saturated fat helps lower LDL cholesterol.
   B. Regular aerobic exercise can increase HDL cholesterol.
   C. Weight loss in overweight individuals may reduce total cholesterol.
   D. Smoking cessation can improve lipid profile.
   E. Excess alcohol leads to high triglyceride levels.

3. Which of the following statements are correct?
   A. A 50-year-old man who underwent CABG 18 months ago presents with a CVA; the target LDL is 100 mg/dL.
   B. A 45-year-old man with diabetes mellitus for five years; the target LDL is <70 mg/dL
   C. A 66-year-old man with a Triglyceride level of 150 mg/dL should be given fenofibrate.
   D. An 85-year-old woman with a history of ischaemic heart disease and otherwise healthy can continue her atorvastatin 20 mg.
   E. A 35-year-old woman with type 1 diabetes for 25 years, the LDL target is < 55 mg/dL.

4. Which of the following statements are correct?
   A. A 65-year-old Sri Lankan's ASCVD risk was assessed using the QRISK3 charts.
   B. The first-line treatment for triglycerides is statins.
   C. Ezetimibe is indicated if LDL golas are not met.
   D. A doubling of transaminases is an indication to stop statins
   E. CPK should be performed before starting statins.

ANSWERS

Question 1
   A. True
   B. False (Ezetimibe inhibits intestinal cholesterol absorption, not bile acid excretion)
   C. True
   D. False (Fibrates primarily lower triglycerides and may increase HDL)
   E. True

Question 2
   A. False
   B. True
   C. True
   D. True
   E. True

Answers: Question 3
   A. False (CVD with second event within 2 years, LDL < 40 mg/dL)
   B. True
   C. False (No need to add fenofibrate and treatment depends on LDL
   D. True (People 85 or older, atorvastatin may reduce non-fatal myocardial infarctions, and if they are already on statins without complications, continue)
   E. False (<70 mg/dL)

Answers: Question 4

   A. False (WHO/ISH chart)
   B. True
   C. True
   D. False (If it rises three times normal, you may withhold statins and observe before restarting statins)
E. False (Only in symptomatic patients)

Medication safety corner

Use of Hydroxychloroquine in Patients with Sulphasalazine Allergy

A patient who developed an allergic reaction to Sulphasalazine was considered for treatment with Hydroxychloroquine and the possibility of cross reactivity and allergy was raised. Allergy to sulphonamides is well recognized and patients present typically with mild reactions like maculopapular rash or urticaria but it can present with life threatening reactions like Steven Johnson syndrome and Toxic Epidermal Necrolysis [1]. However hypersensitivity reactions are rare, reported in 3% [1].

Introduction

Sulfasalazine and hydroxychloroquine are both widely used disease-modifying anti-rheumatic drugs (DMARDs) prescribed for inflammatory conditions such as rheumatoid arthritis (RA) and other autoimmune diseases.

These medicines have distinct mechanisms of action and chemical structures, but there are concerns about potential cross-reactivity and hypersensitivity reactions in patients with a history of previous allergy to sulphonamides.

Hydroxychloroquine belong to the class of drugs known as 4-aminoquinolines, and are closely related to quinine. It is an established therapy for several rheumatological disorders, and it was proposed as a possible treatment for the coronavirus disease 2019 (COVID 19) although randomised trials did not prove any benefit [2]. Sulfasalazine is a prodrug and acts as an anti-inflammatory drug which is used to treat rheumatological conditions as well [3]. Both hydroxychloroquine and sulphasalazine are used currently as off label treatment by clinicians for joint symptoms in chikungunya despite not having any evidence of efficacy and exposing patient to the risk of adverse effects.

Sulfonamides

Sulfonamides are classified into three distinct groups based on their chemical structure and functional groups (Figure 1). The first group, sulfonylarylamines, consists of a sulfonamide moiety directly attached to a benzene ring, with an unsubstituted amine ($-NH_2$) at the N4 position. This structural feature is found in sulfanilamide, which is known for its potential to cause immune-mediated hypersensitivity reactions. The second group, non-sulfonylarylamines, includes compounds where the sulfonamide moiety is attached to a benzene ring or other cyclic structures but lacks the N4 amine group. The third group consists of sulfonamide-containing medicines in which the sulfonamide moiety is not directly attached to a benzene ring, making them structurally distinct from sulfonylarylamines and non-sulfonylarylamines [4].

Sulfasalazine is classified as a non-antibiotic sulfonamide but is structurally related to sulfonylarylamine antibiotics due to the presence of a sulfonylarylamine group [3].

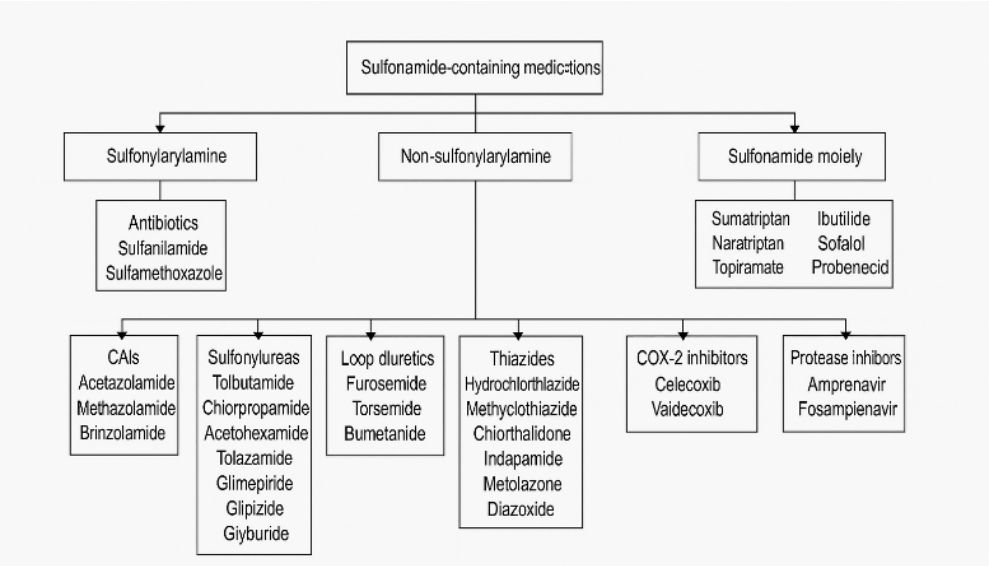

Figure 1: Classification of Sulfonamide

Allergic mechanisms

The exact mechanisms underlying sulfonamide hypersensitivity are not fully understood, but certain key principles have been identified. The term sulfonamide refers to a sulfone group linked to an amine group (Figure 2). Notably, all antibiotic sulfonamides are classified as arylamines which is the main culprit in hypersensitivity immune mediated hypersensitivity reactions [4].

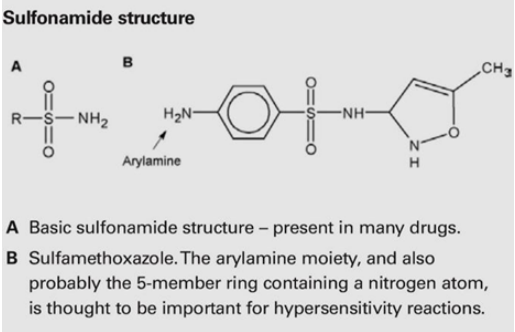

Figure 2: Sulfonamide structure

Like many small chemical allergens, sulfonamides likely require metabolism or haptenation to become immunogenic. During metabolism, the cytochrome P450 enzyme system oxidizes the arylamine group, producing a hydroxylamine intermediate, which is typically neutralized by glutathione and subsequently excreted.

However, if the glutathione detoxification pathway is saturated, excess hydroxylamine can bind to endogenous proteins, triggering hypersensitivity reactions. Additionally, other reactive metabolites have been identified, which may contribute to hypersensitivity by generating immunogenic epitopes for T cells and antibodies, or by exerting direct cytotoxic effects on lymphocytes and other immune cells [1].

Two main types of reactions have been identified. The first is an IgE-mediated immunologic reaction, which requires a 5- or 6-membered aromatic heterocyclic ring at the sulfonamide-N1 position. This reaction typically presents as a maculopapular rash or urticaria within 1–3 days of drug exposure and resolves upon discontinuation, but anaphylaxis may occur with repeat exposure. The second is a delayed hypersensitivity reaction, which requires the amine (-NH_2) at the N4 position and manifests as fever and a non-urticarial rash that may progress to erythema multiforme and multi-organ toxicity within 7–14 days., Non-sulfonylarylamines and other sulfonamide-containing medicines do not share the same risk of hypersensitivity due to chemical and metabolic differences.

Cross-reactivity

Sulfonamide (SO_2-NH_2) groups are present in a range of medicines, including antibiotics like sulfamethoxazole, as well as diuretics, antidiabetics, and analgesics (Figure 3). Previously, adverse reactions to these drugs were collectively labeled as 'sulfa allergy,' leading to the general avoidance of all sulfonamide-containing medicines. However, findings from epidemiological studies, in vitro research, and skin tests suggest that true cross-reactivity between sulfonamide antibiotics and non-antibiotics is uncommon due to their structural differences. Instead, cross-reactivity is primarily observed among aromatic sulfonamides [1]. Aromatic sulfonamide antibiotics feature an aromatic amine group at the N4 position and a substituted ring at the N1 position. (Figure 3).

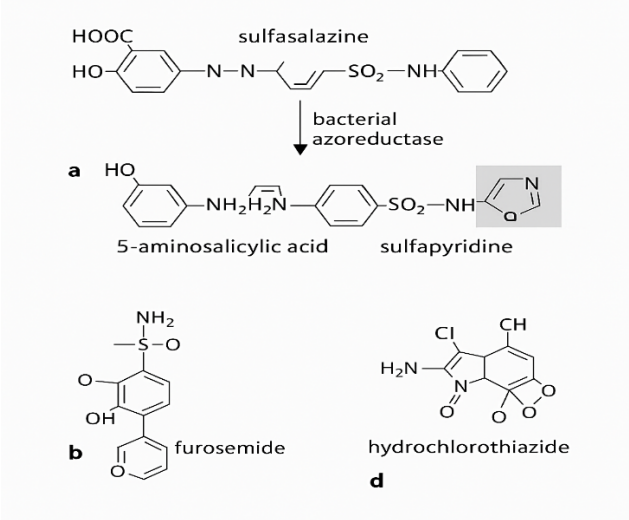

Figure 3: Sulfasalazine Cleavage and Different Sulfonamide Structures

This substituted ring is absent in non-aromatic amines such as furosemide, thiazide diuretics, certain antidiabetic drugs, and celecoxib. But it is present in the anti-inflammatory drug sulfasalazine. It

undergoes metabolism in the colon by the bacterial enzyme azoreductase, breaking down into 5-aminosalicylic acid and sulfapyridine, an aromatic sulfonamide (Figure 3). Due to these structural similarities, significant cross-reactivity is observed among aromatic sulfonamides sulfamethaxole, sulfadiazine, and sulfazalazine [3]. A comprehensive review of relevant studies has debunked the belief that cross-reactivity occurs between sulfonylarylamines and other sulfonamide drugs. This has also been confirmed through studies examining sulfamethoxazole-specific T cell clones, murine T cell hybridoma cells expressing sulfamethoxazole-specific T cell receptors, and Peripheral blood mononuclear cells assays [3].

Hydroxychloroquine and Hydroxychloroquine sulphate do not contain this sulfonamide component (Figure 4). Therefore it is unlikely that they will cross react with Sulfasalazine or other Sulfonamides (Figure 5). But the fact that patients with a history of an allergic reaction to one medicine are generally more prone to develop hypersensitivity to other medicines , even if they are structurally unrelated, possibility of an allergic reaction should always be considered when prescribing [3]. To support this, a retrospective cohort study done in United Kingdom, showed that among people with a prior hypersensitivity reaction to a sulfonamide antibiotic, the risk of an allergic reaction occurring after receiving a non-antibiotic sulphonamide was lower compared to the risk of an allergic reaction occurring after receiving a penicillin [6].

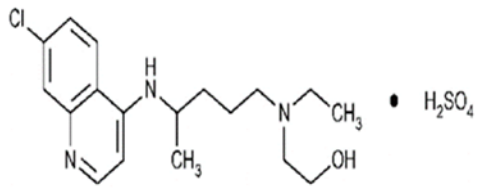

Figure 4: Hydroxychloroquine Sulphate Structure

Common examples of arylamine and non-arylamine sulfonamides

Drug groups	Cross-reactivity
Sulfonamide antibiotics (sulfonylarlamines sulfamethoxazole sulfadiazine sulfadoxine sulfacetamide sulfasalazine (contains sulfapyridine)	Allergic cross-reactivity within this group possible
Sulfonamide antiretrovirals (sulfonylarlamines) amprenavir fosamprenavir	Allergic cross-reactivity with sulfonamide antibotics is likely on structural grounds but has not been established
Non-antibiotic sulfonamide drugs (non-sulfonylarylaminins) frusemide hydrochlorothiazide gliclazide	Current evidence suggests that allergy to sulfonamide antibiptics is not associated with increased risk of allergy to these drugs
Sulfhydryl drugss penicillin piroxicam	No relationship to sulfonamide allergy
Sulfate drugs morphine sulfate	No relationship to sulfonamide allergy

Figure 5: Table of Arylamines and Non-Arylamine Sulfonamides

Conclusion

Sulfasalazine and hydroxychloroquine are both DMARDs used for inflammatory conditions like rheumatoid arthritis. While sulfasalazine contains an aromatic sulfonamide group, hydroxychloroquine does not, making cross-reactivity between them unlikely. However, patients with a history of drug allergies may still have a higher risk of

hypersensitivity to other medications. Therefore, careful monitoring is recommended when prescribing these medicines to individuals with known allergies.

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Regulatory News

From the National Medicines Regulatory Authority (NMRA)

Information on new medicines registered

Melatonin

Dosage form: Film coated Tablet 3mg

Pharmacotherapeutic group: Melatonin Receptor Agonist

ATC code: N05CH01

Pharmacodynamic properties

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. Melatonin has a hypnotic / sedative effect and increases propensity for sleep. Melatonin administered earlier or later than the nocturnal peak in natural melatonin secretion in the body can respectively, advance or delay the circadian rhythmicity of melatonin secretion. Administration of melatonin at bedtime at destination following air travel hastens resynchronization of circadian rhythmicity from 'departure time' to 'destination time',and ameliorates 'jet-lag'.

Pharmacokinetic properties:

Absorption: Orally administered melatonin is almost completely absorbed. Oral bioavailability is about15%, owing to first-pass metabolism of about 85%.

Distribution: melatonin is distributed in all body fluids and is accessible at all tissues. The protein binding of melatonin is approximately 50 – 60%. Melatonin primarily binds to albumin, though also binds alpha1-acid glycoprotein; binding to other plasma proteins is limited.

Metabolism: Cytochrome P450 enzymes, CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance.

Elimination: Metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates

Plasma elimination half-life (T1⁄2) is ~ 45 minutes in healthy adults.

Indication and Dosage:

Jet lag after air travel: For an adult, 3 mg to be taken at the habitual bedtime after arrival at destination once daily as the first dose, increased if necessary to 6 mg for up to 5 days. Doses should not be taken before 8pm or after 4am. Maximum of 16 treatment courses per year.

Insomnia in adults: For adults 55 years and over with primary insomnia: 2 mg once daily for up to 13 weeks, dose to be taken 1–2 hours before bedtime.

Insomnia in children: In children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD), melatonin is indicated where sleep hygiene measures have been insufficient. The recommended starting daily dose is 2 mg of melatonin. If an inadequate response has been observed, the daily dose can be increased to 5 mg, with a maximal dose of 10 mg. The patient should be monitored at regular intervals (at least every 6 months) to check that melatonin is still the most appropriate treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. There is no relevant use of melatonin in children aged 0 to 2 years for the treatment of insomnia.

Warnings and Precautions:

Melatonin may cause drowsiness and should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety such as driving or operating machinery. It may increase seizure frequency in epileptic patients and in children and adolescents with multiple neurological defects.

Exacerbation of autoimmune diseases has been reported, and melatonin is not recommended in patients with autoimmune diseases. Blood glucose control may be impaired for several hours in diabetes. Not recommended for use in patients with severe renal impairment or moderate or severe hepatic impairment. Not recommended in women and men planning pregnancy, during pregnancy and breast-feeding.

Interactions:

Drug interactions can occur with CYP enzyme inhibitors (eg. quinolones, cimetidine) and inducers (such as carbamazepine and rifampicin) and anticoagulation activity of warfarin. Melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. zolpidem, zopiclone).

Adverse effects:

drowsiness, sedation, blood and lymphatic system disorders, Immune system disorders, Psychiatric disorders, Musculo-skeletal and connective tissue disorders

(Prepared based on information in the Product Information leaflet approved by the NMRA)

References

1. Specification of product characteristics approved by NMRA
2. Specification of product characteristics approved in Australia https://www.tga.gov.au/sites/default/files/auspar-melatonin-201027-pi.pdf (Accessed 10 February 2025).

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic class / use(s)
Ceftazidime + Avibactum	Zavicefta	Injection, 2 g + 0.5 g	ACS Dobfar, Italy	…	Complicated intra-abdominal infection
Pembrolizumab	Pembroxim	Injection, 100 mg/4 mL	Beacon, Bangladesh	Emerchemie	Melanoma
Daratumumab	Darzalex	Infusion, 400 mg/20 mL	Cilag, Switzerland	Pettah Pharmacy	Multiple myeloma
Rizatriptan	Rizy 5	Tablet, 5 mg	Celogen, Sri Lanka	Hemas	Acute migraine
Dabigatran	Dabrinex 110	Capsule, 110 mg	Hetero Labs, India	Mansel	Thrombin inhibitor
Halobetasol propionate	Halovate	Ointment 0.05%	Glenmark, India	Sunshine	Topical corticosteroid
Eflornithine	Depilus	Cream, 13.9%	Atco, Pakistan	Morison	Antiprotozoal
Luliconazole	Lanalok	Cream 1%	Blossom, India	George Steuart	Antifungal
Tazarotene	Glentaz	Gel, 0.05	Glenmark, India	Hemas	Plaque psoriasis

Compiled by Chinta Abayawardana.

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