



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



Reference: EDP12082024/01

Enquiries:

Contract queries:

Ms Marione Schonfeldt

E-mail:

marione.schonfeldt@health.gov.za

Stock queries:

Ms Babalwa Melitafa

E-mail:

Babalwa.Melitafa@health.gov.za

Clinical queries:

Essential Drugs Programme

E-mail: SAEDP@health.gov.za

NOTICE: ARIPIRAZOLE FOR THIRD-LINE TREATMENT OF SCHIZOPHRENIA IN ADULTS

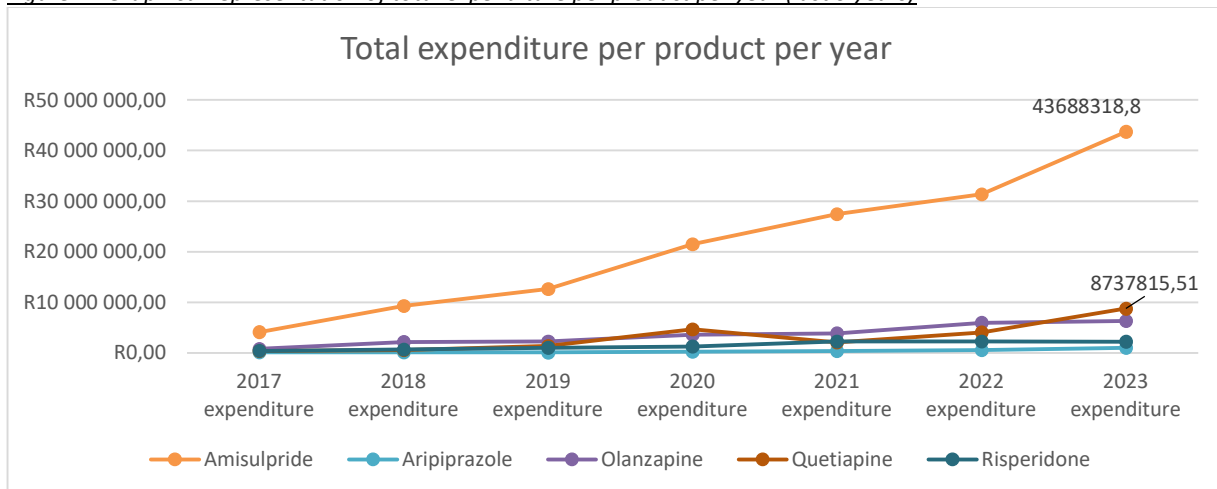
The Tertiary and Quaternary Level Essential Medicines List (EML) previously recommended amisulpride for schizophrenia in adults failing first- and second-line antipsychotics, and who had metabolic concerns which precludes the use of clozapine. Aripiprazole was included as a third-line agent for schizophrenia in children and adolescents with metabolic concerns.

A recent analysis of third-line schizophrenia management undertaken by the Tertiary and Quaternary Expert Review Committee found inter alia that expenditure on amisulpride had substantially increased over the last five years, exceeding the expenditure of other atypical antipsychotics in the public sector (See table 1,2 and figure 1).

Table 1: Total expenditure per product per year (last 5 years)

	Amisulpride	Aripiprazole	Olanzapine	Quetiapine	Risperidone
2017 expenditure	R4,082,677.50	R90,292.07	R789,712.81	R344,854.60	R376,117.00
2018 expenditure	R9,257,223.20	R119,206.72	R2,147,779.23	R523,295.44	R647,161.00
2019 expenditure	R12,605,714.40	R68,027.70	R2,278,034.45	R1,336,065.25	R1,000,203.00
2020 expenditure	R21,437,517.80	R233,889.99	R3,551,060.09	R4,601,676.03	R1,259,920.00
2021 expenditure	R27,437,437.10	R332,572.99	R3,847,584.06	R2,079,266.56	R2,274,024.00
2022 expenditure	R31,339,456.80	R546,066.49	R5,938,265.98	R4,030,990.55	R2,262,710.00
2023 expenditure	R43,688,318.80	R986,195.33	R6,308,106.28	R8,737,815.51	R2,204,942.00

Figure 1: Graphical representation of total expenditure per product per year (last 5 years)



NOTICE: ARIPIPRAZOLE FOR THIRD-LINE SCHIZOPHRENIA

Table 2: Comparative cost per patient per year at lower and higher target doses

Medicine Pack short Description	Price*	Dose#	Cost per day	Cost per month	Cost per year
Amisulpride; 200mg; Tablet; 30 Tablets	R186.50	400mg/day	R12.43	R348.13	R4,538.17
		800mg/day	R24.87	R696.27	R9,076.33
Quetiapine; 200mg; Tablet; 60 Tablets	R48.83	400mg/day	R1.63	R45.57	R594.10
Quetiapine; 300mg; Tablet; 60 Tablets (2) Quetiapine; 200mg; Tablet; 60 Tablets (1)	R67.33	800mg/day	R3.06	R85.63	R1,116.23
Aripiprazole; 15mg; Tablet; 30 Tablets	R47.43	15mg/day	R1.58	R44.27	R577.07
		30mg/day	R3.16	R88.54	R1,154.13
Olanzapine; 10mg; Tablet; 28 Tablets	R14.39	10mg/day	R0.51	R14.39	R187.58
		20mg/day	R1,03	R28.78	R375.17
Risperidone; 2mg; Tablet; 30 Tablets	R5.59	4mg/day	R0.37	R10.43	R136.02
Risperidone; 3mg; Tablet; 30 Tablets	R7.38	6mg/day	R0.49	R13.78	R179.58

*Master Health Product List: February 2024

#International Consensus Study of Antipsychotic Dosingⁱ

Due to the high cost of amisulpride and resultant expenditure, consideration was given to a possible alternative third-line agent for the treatment of schizophrenia spectrum disorders where there is concern of metabolic adverse effects from other atypical antipsychotics. Aripiprazole was proposed as it is already included on the EML for children and adolescents for this indication, and has become more affordable over the past few years. Quetiapine was also considered due to its comparative pricing to aripiprazole and it already being on the EML as third-line treatment for bipolar disorder.

Technical reviews were therefore conducted for aripiprazole and quetiapine (*see table 3 below*). Due to its favorable metabolic profile, aripiprazole is now recommended for third-line schizophrenia for adults as well as children and adolescents with metabolic concerns, as a step before amisulpride. As quetiapine showed no benefit over first- and second-line agents, it was not recommended for this indication.

Table 3: Updated recommendations

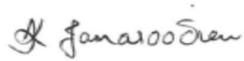
ATC CODE	MEDICINE	INDICATION	NEMLC RECOMMENDATION	LINK TO REVIEW
N05AL05	Amisulpride	Fourth-line schizophrenia	Approved for use as an appropriate alternative to existing agents in patients with schizophrenia failing third-line schizophrenia therapy options.	See aripiprazole review
N05AX12	Aripiprazole	Third-line schizophrenia	Approved for use as an appropriate alternative to existing agents in patients with schizophrenia failing first- and second-line schizophrenia therapy options, and where clozapine not an option due to metabolic effects (weight gain, type II diabetes mellitus), as a step before amisulpride.	https://www.health.gov.za/wp-content/uploads/2024/06/Aripiprazole-3rd-line_4N_May_final.pdf
N05AH04	Quetiapine	Third-line schizophrenia	Not Approved Aripiprazole approved for this indication.	https://www.health.gov.za/wp-content/uploads/2024/06/Quetiapine-3rd-line_4N_May-2024_final.pdf

A stepwise medication guideline for schizophrenia incorporating aripiprazole is attached below in annexure 1 (also available at: https://www.health.gov.za/wp-content/uploads/2024/06/Schizophrenia-Rx-algorithm-4N-May-24_final.pdf).

NOTICE: ARIPIRAZOLE FOR THIRD-LINE SCHIZOPHRENIA

Provinces and Healthcare Facilities are requested to distribute and communicate this information in consultation with the Pharmaceutical and Therapeutics Committees. Kindly share with all healthcare professionals and relevant stakeholders.

Kind regards,



MS KHADIJA JAMALOODIEN
CHIEF DIRECTOR: SECTOR-WIDE PROCUREMENT
DATE: 13 August 2024

NOTICE: ARIPIPRAZOLE FOR THIRD-LINE SCHIZOPHRENIA

For rapid tranquillization see Adult Hospital STGs Chapter 15.1, Aggressive disruptive behaviour.

Switching antipsychotic medicines should not be considered for patients who are well controlled.

STEP 1

TREATMENT INITIATION
<ul style="list-style-type: none">• Haloperidol, oral.<ul style="list-style-type: none">» 0.75 - 1.5 mg daily.» Increase to 5 mg daily (according to tolerability and clinical response).
IF GOOD RESPONSE/TOLERABILITY, OR PATIENT PREFERENCE DEPOT ANTIPSYCHOTIC, E.G.
<ul style="list-style-type: none">• Flupenthixol deconate, IM.<ul style="list-style-type: none">» 10 - 40 mg every 4 weeks (initial dose: 10 mg). <p>OR</p> <ul style="list-style-type: none">• Zuclopenthixol deconate, IM.<ul style="list-style-type: none">» 100 - 400 mg every 4 weeks (initial dose: 100 mg).

STEP 2

IF POOR RESPONSE/TOLERABILITY, OR HIGH-RISK OF TARDIVE DYSKINESIA/EXTRAPYRAMIDAL EFFECTS*
<ul style="list-style-type: none">• Risperidone, oral.<ul style="list-style-type: none">» Initial dose: 2 - 4 mg at night. (Assess efficacy after 4 - 6 weeks)» Maximum dose: 6 mg daily.
IF POOR RESPONSE/TOLERABILITY TO HALOPERIDOL/RISPERIDONE
<ul style="list-style-type: none">• Olanzapine, oral.<ul style="list-style-type: none">» Initial dose: 5 mg at night, increase to 10 mg at night.» Maximum dose: 20 mg at night.

STEP 3

IF POOR RESPONSE/TOLERABILITY TO OLANZAPINE
<ul style="list-style-type: none">• Clozapine, oral (specialist initiated, preferably as inpatient):<ul style="list-style-type: none">» Initial dose: 12.5–25 mg at night. (Usual dose: 200–450 mg per day in 2 divided doses)» Maximum dose: 900 mg/day in 2 divided doses <p>OR</p>
IF POOR RESPONSE TO OLANZAPINE AND CLOZAPINE IS NOT AN OPTION DUE TO METABOLIC EFFECTS (WEIGHT GAIN, TYPE 2 DIABETES)
<ul style="list-style-type: none">• Aripiprazole, oral (specialist initiated).

STEP 4

IF POOR RESPONSE TO ARIPIPRAZOLE
<ul style="list-style-type: none">• Amisulpride, oral (specialist initiated).

Notes:

- Decisions in the algorithm steps are driven largely by price of individual medicines.
- *Chlorpromazine, oral is included in PHC and Adult Hospital Level STGs and EML as an alternative to risperidone. Due to its high cost and side effect profile, it has been excluded from this treatment algorithm but may be used as an option if required. Patients who are currently stable on chlorpromazine should continue on this therapy.

ⁱ Gardner DM Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. American Journal of Psychiatry. 2010. 167(6): 686-693.