SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MITHYRO 25/50/75/100 µg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MITHYRO 25 µg contains levothyroxine sodium hydrate equivalent to levothyroxine sodium 0,025 mg per tablet.

MITHYRO 50 µg contains levothyroxine sodium hydrate equivalent to levothyroxine sodium 0,050 mg per tablet.

MITHYRO 75 µg contains levothyroxine sodium hydrate equivalent to levothyroxine sodium 0,075 mg per tablet.

MITHYRO 100 µg contains levothyroxine sodium hydrate equivalent to levothyroxine sodium 0,100 mg per tablet.

Excipients with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1

Sugar free

3. PHARMACEUTICAL FORM

Tablets

White tablets engraved with "25", "50", "75" or "100" on one side, depending on the respective strength.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MITHYRO is indicated for untreated hypothyroidism.

4.2 Posology and method of administration

If the dose of MITHYRO is increased too rapidly, symptoms such as diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia may occur and the dosage must be reduced or withheld for a day or two, then restarted at a lower level.

Posology

Adults

Initially 50 µg to 100 µg daily, preferably taken before breakfast or the first meal of the day. Adjust at three to four week intervals by 50 micrograms until normal metabolism is steadily maintained. The final daily dose may be up to 100 micrograms to 300 micrograms.

Missed dosage: If a scheduled daily dose is missed, the dose should be taken as soon as the patient remembers, unless it is almost time for the patient's next dose. Two doses should not be taken together.
The dose of MITHYRO for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

Special populations:

Elderly

As for patients aged over 50 years.

For patients over 50 years, initially, it is not advisable to exceed 50 micrograms daily. In this condition, the daily dose may be increased by 50 micrograms at intervals of every 3 to 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 micrograms to 200 micrograms.

Patients over 50 years with cardiac disease

Where there is cardiac disease, 25 micrograms daily or 50 micrograms on alternate days is more suitable. In these conditions, the daily dose may be increased by 25 micrograms at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 micrograms to 200 micrograms
For patients aged over 50 years, with or without cardiac disease, clinical response is probably a more acceptable criteria of dosage rather than serum levels.

Paediatric population

The maintenance dose is generally 100 micrograms to 150 micrograms per m^2 body surface area. The dose for children depends on their age, weight and the condition being treated.
Regular monitoring is required to make sure he/she gets the right dose. Infants should be given the total daily dose at least half an hour before the first meal of the day.

Congenital hypothyroidism in infants

For neonates and infants with congenital hypothyroidism, where rapid replacement is important, the initial recommended dosage is 10 micrograms to 15 micrograms per kg body weight per day for the first 3 months. Thereafter, the dose should be adjusted individually according to the clinical findings and thyroid hormone and TSH values.

Juvenile myxoedema in children

The initial recommended dosage is 25 micrograms daily. In such conditions, the daily dose may be increased by 25 micrograms at intervals of every 2 to 4 weeks, until mild symptoms of hyperthyroidism are seen. The dose will then be reduced slightly.

When applicable

Tablets are to be disintegrated in some water (10 ml to 15 ml) and the resultant suspension, which must be prepared freshly as required, is to be administered with some more liquid (5 ml to 10 ml).

Method of administration

Oral

4.3 Contraindications

MITHYRO is contraindicated in:

- Patients with untreated hyperthyroidism.
- Patients with hypersensitivity to levothyroxine sodium or to any of the excipients of MITHYRO (see section 6.1).
- Untreated adrenal insufficiency, untreated pituitary insufficiency.
- Treatment must not be initiated in acute myocardial infarction, acute myocarditis, and acute pancarditis.

4.4 Special warnings and precautions for use

- At the beginning of treatment, ordinary therapeutic doses may cause anginal pain, palpitations and cramps in the skeletal muscle.
- Before starting therapy with MITHYRO the following diseases should be excluded or treated: coronary insufficiency, angina pectoris, arteriosclerosis, hypertension, pituitary insufficiency, adrenal insufficiency, thyroid autonomy.

- Even slight medicine-induced hyperthyroidism must be avoided in patients with coronary failure, cardiac insufficiency or tachycardiac dysrhythmias. Hence frequent checks of thyroid hormone parameters must be made in these cases.
- In the case of secondary hypothyroidism, the cause must be determined before replacement therapy is given and if necessary, replacement treatment of a compensated adrenal insufficiency must be commenced.
- Where thyroid autonomy is suspected, a TRH test should be carried out or a suppression scintigram obtained before treatment.
- In postmenopausal women with hypothyroidism and an increased risk of osteoporosis, supraphysiological serum levels of MITHYRO should be avoided, and, therefore, thyroid function should be checked regularly.
- Thyroid storm (or thyrotoxic crisis) is a medical emergency and has been occasionally reported after massive or chronic intoxication. Convulsions, cardiac dysrhythmias, heart failure, coma and death have occurred (see section 4.9).
- MITHYRO has a narrow therapeutic index. Appropriate MITHYRO dosage is based upon clinical assessment and laboratory monitoring of thyroid function tests. During the initial titration period, careful dosage titration and monitoring is necessary to avoid the consequences of under- or over-treatment. The symptoms of excessive MITHYRO dosage are the same as many features of endogenous thyrotoxicosis.
- Treatment with MITHYRO in patients with panhypopituitarism or other causes predisposing to adrenal insufficiency may cause reactions including dizziness, weakness, malaise, weight loss, hypotension and adrenal crisis. It is advisable to initiate corticosteroid therapy before giving MITHYRO in these cases.
- Subclinical hyperthyroidism may be associated with bone loss. To minimise the risk of osteoporosis, dosage of MITHYRO should be titrated to the lowest possible effective level.
- It is especially important that children with hypothyroidism have their dosage individualized and treatment monitored.

- Parents of children receiving MITHYRO should be advised that partial loss of hair may occur during the first few months of therapy, but this effect is usually transient and subsequent regrowth may occur.
- Special care is needed in the elderly and in patients with symptoms of myocardial insufficiency or ECG evidence of myocardial infarction or ischaemia and also those with diabetes mellitus or insipidus.
- MITHYRO raises blood sugar levels and this may upset the stability of patients receiving antidiabetic medicines.
- Care is required when MITHYRO is administered to patients with known history of epilepsy. Seizures have been reported in association with the initiation of levothyroxine sodium therapy and may be related to the effect of thyroid hormone on seizure threshold.
- Haemodynamic parameters should be monitored when MITHYRO is initiated in very low birth weight preterm neonates as circulatory collapse may occur due to the immature adrenal function.

4.5 Interaction with other medicines and other forms of interaction

Warfarin: MITHYRO increases the effect of warfarin and it may be necessary to reduce the dose of warfarin if excessive hypoprothrombinaemia and bleeding are to be avoided. The INR should be monitored.

Phenytoin and carbamazepine: Phenytoin levels may be increased by MITHYRO. Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of MITHYRO and may displace thyroxine from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter thyroxine sodium dose requirements.

Digoxin: If co-administered with digoxin, adjustment of dosage may be necessary.

Sympathomimetic medicines: The effects of sympathomimetic medicines are also enhanced. MITHYRO increases receptor sensitivity to catecholamines thus accelerating the response to tricyclic antidepressants

(e.g., amitriptyline, imipramine).

Cholestyramine: Cholestyramine given concurrently reduces the gastrointestinal absorption of MITHYRO.

Other medicines: A number of other medicines may decrease the absorption of MITHYRO, and therefore increase MITHYRO dosage requirements including antacids (e.g., aluminium hydroxide), proton pump inhibitors, cimetidine, bile acid sequestrants (e.g., colestipol), cation exchange resins (e.g., kayexalate), sucralfate, calcium carbonate and ferrous sulphate (administration should be separated by 4 to 5 hours).
Co-administration of oral contraceptives, as well as a number of other medicines, including oestrogen, tamoxifen, clofibrate, methadone, and 5-fluorouracil may increase serum concentration of thyroxine-binding globulin, and therefore increase MITHYRO dosage requirements.
A number of medicines may decrease serum concentration of thyroxine-binding globulin, and therefore decrease MITHYRO dosage requirements, including androgens and anabolic steroids.

Imatinib: Treatment with imatinib was associated with increased MITHYRO dosage requirements in hypothyroid patients.

Amiodarone: Treatment with amiodarone has been associated with multiple effects on thyroid function including increased MITHYRO dosage requirements in hypothyroid patients.

Thyroid function tests: A number of medicines may affect thyroid function tests and this should be borne in mind when monitoring a patient on MITHYRO therapy.

Antibacterials: Enzyme induction by rifampicin enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Oral ciprofloxacin can lead to the development of hypothyroidism in stable patients receiving MITHYRO.

Antidiabetics: As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any medicine treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their insulin or oral hypoglycaemic requirements.

Antidepressants: Some medicines such as lithium act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism. The effects of MITHYRO in hypothyroid patients may be decreased by use with sertraline, and the dose of MITHYRO may need to be increased.

Antivirals: An increased dose of MITHYRO is necessary with ritonavir whereas a decreased dose is needed with indinavir.

Beta-blockers: Plasma concentrations of propranolol are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance and hypothyroid patients receiving chronic propranolol therapy have a reduction in plasma-propranolol concentrations when given MITHYRO treatment.

General anaesthetics: Severe hypertension and tachycardia can occur when ketamine is used in patients taking MITHYRO.

Antimalarials: Increased thyroid-stimulating hormone concentration can occur after the use of chloroquine with proguanil for malaria prophylaxis.

NSAIDs: Falsely low concentrations of levothyroxine (T4) or tri-iodothyronine (T3) can occur during treatment with some anti-inflammatory medicines. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.

Soya-based infant formula: Soya-based infant formulas may impair absorption of MITHYRO, and frequent testing may be needed, particularly when there are changes in formula.

Simvastatin: Increased thyroid stimulating hormone concentrations, requiring increased doses of MITHYRO, can occur when simvastatin is used.

Furosemide: Furosemide in high doses (250 mg) can displace levothyroxine sodium as contained in MITHYRO, resulting in an elevated free-thyroxine (T4) fraction.

Anti-obesity medicines: Anti-obesity medicines, such as orlistat may decrease levothyroxine absorption which may result in hypothyroidism (monitor for changes in thyroid function).

4.6 Fertility, pregnancy and lactation

Pregnancy

MITHYRO has been taken by pregnant women and women of childbearing age without any form of definite disturbances in the reproductive process having been observed. Thyroid hypo- or hyperactivity in the mother may, however, unfavourably influence the foetal and postnatal development, therefore MITHYRO dosage may need to be adjusted during pregnancy.

Breastfeeding

MITHYRO is excreted in breast milk and this may be sufficient to interfere with neonatal screening for hypothyroidism. It is very important to monitor thyroid function in the mother as well as in the infant regularly.

4.7 Effects on ability to drive and use machines

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that MITHYRO does not adversely affect their ability to do so safely.

4.8 Undesirable effects

The following effects are indicative of excessive dosage, and usually disappear on reduction of dosage or withdrawal of treatment for a few days.

MedDRA System Organ Class	Less frequent	Frequency unknown
Immune system disorders		Hypersensitivity reactions such as skin rash, pruritus, eosinophilia, fever and liver dysfunction
Endocrine disorders	Hyperthyroidism, hypothyroidism	Heat intolerance, flushing, thyrotoxic crisis[1]
Metabolism and nutrition disorders		Increased appetite
Psychiatric disorders		Excitability, restlessness, insomnia, confusion, agitation
Nervous system disorders		Headache, tremors, seizure, cephalalgia. Cases of pseudotumour cerebri (benign intracranial hypertension) have been reported, especially in children

Cardiac disorders		Anginal pain, cardiac dysrhythmias, palpitations, tachycardia, heart failure, myocardial infarction
Vascular disorders		Increased blood pressure
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders		Abdominal cramps, nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders		Sweating, hair loss
Musculoskeletal, connective tissue and bone disorders		Cramps in the skeletal muscle, muscular weakness, decreased bone mineral density. Excessive dose may result in craniosynostosis in infants, and premature closure of epiphyses in children with compromised adult height, arthralgia
Reproductive system and breast disorders		Menstrual irregularity, impaired fertility
General disorders and administration site conditions		Fatigue, excessive loss of weight, malaise

[1] Some patients may experience a severe reaction to high levels of thyroid hormone. This is called a "thyroid crisis" with any of the following symptoms: Hyperpyrexia, tachycardia, dysrhythmia, hypotension, cardiac

failure, jaundice, confusion, seizure and coma.

Paediatric population

Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

In addition to exaggeration of side effects, the following symptoms may be seen: agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, dysrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions. In addition to all known side effects, thyroid storm (or thyrotoxic crisis) a medical emergency, may occur and require urgent medical attention as soon as possible. Some of the signs of thyrotoxicosis that have been reported include fever, dysrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications and coma.

The appearance of clinical hyperthyroidism may be delayed for up to five days.

Treatment

The goal of therapy is restoration of clinical and biochemical euthyroid state by omitting or reducing the thyroxine dosage and other measures as needed depending on clinical status.

Treatment is symptomatic and tachycardia has been controlled in an adult by a suitable beta blocking medicine and other symptoms by a suitable benzodiazepine as appropriate.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group:	Thyroid hormones
Category and class:	A 21.3 Thyroid preparations
ATC Code:	H03AA01

5.1 Pharmacodynamic properties

Thyroxine (T4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone tri-iodothyronine (T3) in peripheral tissues. The precise signals controlling the conversion of T4 to T3 within the cell are not known. The thyroid hormones are required for normal growth and development, particularly of the nervous system. They increase the resting or basal metabolic rate of the whole organism and have stimulatory effects on the heart, skeletal muscle, liver and kidney. Thyroid hormones enhance lipolysis and the utilisation of carbohydrate. 100 µg thyroxine is equivalent in activity to 20 µg to 30 µg liothyronine/tri-iodothyronine or 60 mg thyroid BP.

5.2 Pharmacokinetic properties

Absorption

Following oral administration the absorption of thyroxine is incomplete and variable especially when taken with food. The amount absorbed increases during fasting conditions.

Distribution

Thyroxine is nearly totally bound to serum protein.

Biotransformation

The main pathway for the metabolism of thyroxine (T4) is its conversion, by de-iodination, to the active metabolite tri-iodothyronine (T3). Further de-iodination of T4 and T3 leads to production of inactive products.

Elimination

Thyroxine is eliminated slowly from the body with a half-life of approximately seven days in a normal person. This may be reduced in hyperthyroid states or increased in hypothyroid patients. In man approximately 20 % to 40 % of thyroxine is eliminated in the faeces and approximately 30 % to 55 % of a dose of thyroxine is excreted in the urine.

Special populations

Subjects with renal insufficiency

Renal disease does not appear to have any significant effect on the disposition of thyroxine.

Subjects with hepatic impairment

Hepatic disease does not appear to have any significant effect on the disposition of thyroxine.

5.3 Preclinical safety data

No non-clinical study was performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose powdered (Arbosel M80)

Sodium croscarmellose

Silicon dioxide colloidal (anhydrous)

Cellulose microcrystalline (Type 101)

Magnesium stearate (vegetable)

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep the tablets in the blisters until required for use.

6.5 Nature and contents of container

MITHYRO tablets are packed in clear transparent PVC/TE/PVDC/Silver Aluminium blisters.

The blisters are further packaged in cardboard boxes. Each cardboard box (BT) contains 30 (2 blister x 15 tablets), 50 (2 blister x 25 tablets), 60 (4 blister x 15 tablets), or 100 tablets (4 blister x 25 tablets), presented in multiple blister strips of 15 or 25 tablets, along with a Patient Information Leaflet.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

Tel. nr: 011 848 3050

8. REGISTRATION NUMBER(S)

MITHYRO 25 µg – 52/21.3/0882

MITHYRO 50 µg – 52/21.3/0883

MITHYRO 75 µg – 52/21.3/0884

MITHYRO 100 µg – 52/21.3/0885

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 October 2023

10. DATE OF REVISION OF THE TEXT

31 October 2023