1.5.5.2 CLEAN AMENDED PROFESSIONAL INFORMATION

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF MEDICINE

ROIDACE 25 µg (tablet)

ROIDACE 50 µg (tablet)

ROIDACE 75 µg (tablet)

ROIDACE 100 µg (tablet)

ROIDACE 200 µg (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each tablet of **ROIDACE** contains 25 µg, 50 µg, 75 µg, 100 µg, or 200 µg of levothyroxine sodium.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ROIDACE 25 µg - round orange colour tablets with score line on one side and "25" debossed on other side of the tablet.

ROIDACE 50 µg - round white colour tablets with score line on one side and "50" debossed on other side of the tablet.

ROIDACE 75 µg - round violet colour tablets with score line on one side and "75" debossed on other side of the tablet.

ROIDACE 100 µg - round yellow colour tablets with score line on one side and "100" debossed on other side of the tablet.

ROIDACE 200 µg - round pink colour tablets with score line on one side and "200" debossed on other side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ROIDACE is indicated for untreated hypothyroidism.

4.2 Posology and method of administration

Posology

If the dose of **ROIDACE** 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.

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 **ROIDACE** for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

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 µg until normal metabolism is steadily maintained. The final daily dose may be up to 100 µg to 300 µg.

Special populations

Elderly

As for patients aged over 50 years.

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

Patients over 50 years with cardiac disease

Where there is cardiac disease, 25 µg daily or 50 µg on alternate days is more suitable. In these conditions, the daily dose may be increased by 25 µg at intervals of every 4 weeks, until stable thyroxine levels are attained. The final daily dose may be up to 50 µg to 200 µg.

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 µg to 150 µg 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 µg to 15 µg 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.

Acquired hypothyroidism in children

For children with acquired hypothyroidism, the initial recommended dosage is 12,5 µg to 50 µg per day. The dose should be increased gradually every 2 to 4 weeks according to the clinical findings and thyroid hormone and TSH values until the full replacement dose is reached.

Juvenile myxoedema in children

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

Method of administration

For oral use.

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Patients with untreated hyperthyroidism.
- 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 onset of treatment, ordinary therapeutic doses may cause anginal pain, palpitations and cramps in the skeletal muscle.

Before initiating therapy with **ROIDACE** 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 **ROIDACE** 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)

ROIDACE has a narrow therapeutic index. Appropriate **ROIDACE** 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 **ROIDACE** dosage are the same as many features of endogenous thyrotoxicosis.

Treatment with **ROIDACE** 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 **ROIDACE** in these cases.

Subclinical hyperthyroidism may be associated with bone loss. To minimise the risk of osteoporosis, dosage of **ROIDACE** should be titrated to the lowest possible effective level.

It is especially important that children with hypothyroidism have their dosage individualised and treatment monitored.

Parents of children receiving **ROIDACE** 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.

ROIDACE raises blood sugar levels and this may upset the stability of patients receiving antidiabetic medicines.

Orlistat may decrease **ROIDACE** absorption which may result in hypothyroidism. To avoid this orlistat and **ROIDACE** should be administered at least 4 hours apart. Regular monitoring for changes in thyroid function is required (see section 4.5).

Patients with myxoedema have an increased sensitivity for thyroid hormones; in these patients the starting dose should be low with slow dosing increments.

ROIDACE absorption is decreased in patients with malabsorption syndromes. It is advised to treat the malabsorption condition to ensure effective **ROIDACE** treatment with regular **ROIDACE** dose.

Use in Pregnancy

If overt hypothyroidism is diagnosed during pregnancy, thyroid function test results should be normalised as rapidly as possible. In newly-diagnosed hypothyroidism in pregnancy, thyroxine dosage should be titrated rapidly, for example 1,5 to 2,0 µg/kg/day may be required for initial replacement. If hypothyroidism has been diagnosed before pregnancy, thyroxine therapy should be optimised before conception and monitored during pregnancy by measurement of serum TSH and thyroxine levels. The thyroxine dose commonly needs incremental adjustments by 4 to 6 weeks of gestation and may require a 25 to 40 % increase in dosage. It is recommended that those levels should be re-evaluated every 3 to 4 weeks during the first and second trimesters, with thyroxine dosage changes as appropriate. The requirement is likely to decrease post-partum.

Monitoring of TSH concentrations can give guidance. TBG (Thyroid-Binding Globulin) increases during pregnancy and therefore total T4 and T3 may appear to be elevated. Measurement of free T4 and T3 may be more appropriate. There is contradictory evidence concerning the passage of T4 and T3 across the

placenta but it is unlikely that the foetus is at risk. Clinical experience does not indicate any adverse effects on the foetus when thyroxine is administered during pregnancy (see section 4.6).

TSH monitoring during pregnancy

During pregnancy, serum levothyroxine levels may decrease with a concomitant increase in serum TSH level to values outside the normal range. Patients taking **ROIDACE** should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of **ROIDACE**. Since postpartum TSH serum levels are similar to preconception values, **ROIDACE** dosage can be reduced to the pre-pregnancy dose (see section 4.6)

4.5 Interaction with other medicines and other forms of interaction

Warfarin: **ROIDACE** 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 **ROIDACE**. Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of **ROIDACE** 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.

ROIDACE 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 **ROIDACE**.

Other medicines: A number of other medicines may decrease the absorption of **ROIDACE**, and therefore increase **ROIDACE** 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 **ROIDACE** dosage requirements.

A number of medicines may decrease serum concentration of thyroxine-binding globulin, and therefore decrease **ROIDACE** dosage requirements, including androgens and anabolic steroids.

Imatinib: Treatment with imatinib was associated with increased levothyroxine sodium as in **ROIDACE** dosage requirements in hypothyroid patients.

Amiodarone: Treatment with amiodarone has been associated with multiple effects on thyroid function including increased **ROIDACE** 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 **ROIDACE** 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 **ROIDACE**.

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 **ROIDACE** in hypothyroid patients may be decreased by use with sertraline, and the dose of **ROIDACE** may need to be increased.

Antivirals: An increased dose of **ROIDACE** 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 **ROIDACE** treatment.

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

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 **ROIDACE**, and frequent testing may be needed, particularly when there are changes in formula.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

ROIDACE 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 **ROIDACE** dosage may need to be adjusted during pregnancy (see section 4.4).

Breastfeeding

ROIDACE 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.

Fertility

There is no available data on the effect of **ROIDACE** on fertility.

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 **ROIDACE** does not adversely affect their ability to do so safely (See section 4.8).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

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

System organ class	**Frequency unknown (cannot be estimated from the available data)**
Immune system disorders	Hypersensitivity reactions, rash, pruritus, anaphylactic reactions, eosinophilia, fever, liver dysfunction
Endocrine disorders	Hyperthyroidism, hypothyroidism, thyrotoxic crisis
Metabolism and nutrition disorders	Increased appetite, loss of weight
Psychiatric disorders	Excitability, restlessness, insomnia, confusion, agitation, anxiety, affect emotional lability, nervousness
Nervous system disorders	Headache, tremors, seizure, cephalalgia.cases of benign intracranial hypertension
Cardiac disorders	Angina pectoris, cardiac dysrhythmias, palpitations, tachycardia, cardiac failure, myocardial infarction
Vascular disorders	Increased blood pressure, flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea

Gastrointestinal disorders	Abdominal pain, nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Hyperhidrosis, hair loss, rash, pruritus, angioedema, urticaria
Musculoskeletal and connective tissue disorders	Muscle spasms, muscular weakness, arthralgia
Reproductive system and breast disorders	Irregular menstruation, infertility
Congenital and familial and genetic disorders	Excessive dose may result in craniosynostosis in infants, and epiphyses premature fusion in children with compromised adult height
General disorders and administrative site conditions	Fatigue, temperature intolerance, pyrexia, malaise, oedema
Investigations	Decreased bone mineral density

b) Paediatric population

Heat intolerance, transient hair loss, benign intracranial hypertension, craniostenosis in infants and premature closure of epiphysis in children.
Cases of benign intracranial hypertension have been reported, especially in children.

Reporting of suspected adverse reactions

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

4.9 Overdose

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.

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

5.1 Pharmacodynamic properties

Category and class: A 21.3 Thyroid preparations

Pharmacotherapeutic group: Thyroid hormones

ATC Code: H03AA01

ROIDACE is a tablet containing the hydrated form of Levothyroxine sodium. The thyroid gland is dependent upon 2 active principles for its main hormone activity these are Levothyroxine (tetraiodothyronine) and Tri-iodothyronine. These closely related iodine containing amino acids are incorporated into the

glycoprotein thyroglobulin. The chief action of these hormones is to increase the rate of cell metabolism. Levothyroxine is deiodinated in peripheral tissues to form Tri-iodothyronine which is thought to be the active tissue form of thyroid hormone. Tri-iodothyronine is certainly more rapid acting and has a shorter duration of action than Levothyroxine. The chief action of Levothyroxine is to increase the rate of cell metabolism.

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

Renal impairment

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

Hepatic impairment

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

pregelatinized starch

colloidal silicon dioxide

talc

magnesium stearate

colourant

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package in order to protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

Tablets are packed in packed in HDPE bottle pack comprises a white coloured bottle along with the white PP cap having induction sealing wad in packs of 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

3 Gwen Lane, 4th Floor,

Sandton,

2031

8 REGISTRATION NUMBER(S)

ROIDACE 25: 56/21.3/0331

ROIDACE 50: 56/21.3/0332

ROIDACE 75: 56/21.3/0333

ROIDACE 100: 56/21.3/0334

ROIDACE 200: 56/21.3/0335

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 February 2024

10 DATE OF REVISION OF THE TEXT