

RAGE THERMO EXTREME

PROFESSIONAL INFORMATION

D 33.7 Combination product. Complementary medicine.

This unregistered medicine has not been evaluated by SAHPRA for its quality, safety or intended use

SCHEDULING STATUS: SO

1. NAME OF THE MEDICINE BIOGEN RAGE THERMO EXTREME capsules.

2. OLIAL ITATIVE AND OLIANTITATIVE COMPOSITION

2. QUALITATIVE AND QUANTITATIVE CONTROSTITION		
Each vegetable capsule contains:		%NRV*
Sinetrol® Xpur (standardised citrus and guarana extra	cts) 225,00 mg	
from: Citrus grandis (L.) Osbeck (Grapefruit) [fruit extract]	101,25 mg	
Paullinia cupana Kunth (Guarana) [seed extract]	22,50 mg	
Citrus sinensis (L.) Osbeck (Sweet orange) [fruit extract]	22,50 mg	
Citrus sinensis (L.) Osbeck (Blood orange) [fruit concentrate]	11,25 mg	
Total Caffeine	75,00 mg	
from: Caffeine Anhydrous	68,13 mg	
Sinetrol® Xpur	5,62 mg	
Yerba Mate	1,25 mg	
Ilex paraguariensis (Yerba Mate) [Leaf; 10:1 extract providing 250 mg DHE]	125,00 mg	
Olea europaea L. (Olive) [Leaf; extract providing 20 % Oleuropein]	25,00 mg	
L-theanine	50,00 mg	
Pantothenic Acid (Vitamin B₅) (from calcium D-pantothenate)	2,30 mg	46 %
BioPerine® Piper nigrum L. (Black pepper) [fruit extract]	2,50 mg	
Chromium (from Chromium picolinate)	50,00 μg	143%
Sugar free		

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vegetable capsules. Size 00 white vegetable capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOGEN RAGE THERMO EXTREME is indicated as an aid to a weight management programme, in conjunction with a balanced diet and exercise program. 4.2 Posology and method of administration

Adults:

Take 2 capsules twice daily, at least 30 minutes before meals or snacks (preferably with breakfast and lunch). If you are training early in the morning, take 2 capsules before your workout and consume a post-workout meal directly after training, or as recommended by your health care provider. Consumption not recommended after 16:00. Consume for 5 consecutive days and take a 2 day break before resuming again.

Do not exceed the recommended dosage.

Elderly:

No specific studies have been performed in older patients, but according to clinical experience dosage adjustment is not required when treating otherwise healthy, older patients. Patient with impaired renal and/or liver function:

In patients with impaired renal and/or liver function no dose recommendations can be given, since no studies have been performed (see also section 4.4).

Children and adolescents:

Not recommended in children and adolescents below the age of 18 years (see section 4.4).

- If you have a hypersensitivity to Grapefruit extract, Guarana, Sweet orange extract, Blood orange extract, Caffeine
 anhydrous, Yerba mate, Olive leaf extract, L-theanine, Vitamin B₅, BioPerine, and Chromium or any of the excipients
- Consult a healthcare provider prior to use if you are pregnant, breastfeeding or have a kidney disorder.
- Consult a healthcare provider prior to use if you are taking other diuretics.
 Not recommended for use in children under the age of 18 years.

4.4 Special warnings and precautions for use

Special care should be taken with BIOGEN RAGE THERMO EXTREME. If you are taking any prescribed medication, please check with your healthcare provider before taking this medicine.

- Please take note of the following:

 Consult a healthcare provider prior to use if you are pregnant, breastfeeding or have a kidney disorder.

 Consult a healthcare provider prior to use if you are taking other diuretics.

 CONTAINS CAFFEINE, Not suitable for children under the age of 18 years.

- CONTAINS CAFFEINE. Not suitable for children under the age of 18 years.
 Not intended as a substitute for sleep.
 Hypertension, glaucoma and/or detrusor instability (overactive bladder syndrome).
 Consult a health care provider prior to use if you have high blood pressure, glaucoma, and/or detrusor instability (overactive bladder syndrome). The caffeine content may increase high blood pressure, increase intraocular pressure, and/or worsen symptoms of incontinence (such as urinary frequency and urgency).
 May reduce blood flow to the heart muscle during exercise, which might lead to cardiovascular complications such as chest pain and irregular heartbeat.
 Patients are advised to discontinue BIOGEN RAGE THERMO EXTREME at least 2 weeks prior to any surgical procedures.

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 Might affect blood glucose levels, which might interfere with blood glucose control in patients with diabetes mellitus (see section 4.5).

 Caution is advised for patients with existing renal or liver impairment.

 Patients with epilepsy should use BIOGEN RAGE THERMO EXTREME with caution.

 Avoid taking with health products or foods that contain caffeine and/or increase blood pressure (e.g. medications, coffee, tea, colas, cocoa, guarana, mate, bitter orange extract, synephrine, cotopamine, ephedra, ephedrine).

 Caffeine has been shown to reduce blood flow to the heart muscle during exercise which might lead to cardiovascular complications such as chest pain, and irregular heartbeat even in healthy individuals. If those symptoms occur, stop use and consult a health care practitioner/health care provider

Nutritional supplementation should not replace a balanced diet. Do not exceed the recommended dose without consulting a healthcare provider.

4.5 Interaction with other medicines and other forms of interaction

No specific drug interaction studies have been performed on BIOGEN RAGE THERMO EXTREME, however, the pharmacokinetic properties of Grapefruit extract, Guarana, Sweet orange extract, Blood orange extract, Caffe anhydrous, Yerba mate, Olive leaf extract, L-theanine, Vitamin B_s, BioPerine, and Chromium have been summ

- Interactions with Medicines

 Consult a health care provider prior to use if you are taking lithium.

 Consumption with other medicines which increase blood pressure (e.g. bitter orange extract, synephrine, octopamine, ephedra, ephedrine) is not recommended.

 Consumption with other caffeine-containing products (e.g. medicines, coffee, tea, colas, cocoa, guarana, maté) is not recommended.

 May potentiate effects of oral hypoglycaemics and may reduce insulin requirement, increasing the risk of hypoglycemia. Dose adjustment of diabetic medicines and glucose monitoring may be necessary.

 Anticonvulsant medicines (such as carbamazepine, ethosuximide, felbamate, phenobarbital, phenytoin or valproate) as in BIOGEN RAGE THERMO EXTREME may decrease the effects of anticonvulsants and increase the risk of seizures.
- BIOGEN RAGE THERMO EXTREME may increase the risk of bleeding when used concomitantly with anticoagulant medicines (such as heparin or warfarin) or antiplatelet medicines (such as aspirin, clopidogrel, dipyridamole or ticlopidine).

- Interactions with Diseases / Impairments

 Patients are advised to discontinue BIOGEN RAGE THERMO EXTREME at least 2 weeks before elective surgical procedures (see section 4.4).

 BIOGEN RAGE THERMO EXTREME and use in Haemophiliacs and patients scheduled for surgery are advised to discontinue use at least 2 weeks before elective surgical procedures (see section 4.4).

 Bivitamins might increase the rate of restenosis after bare metal stent placement.

Interactions with Foods

Vitamins, minerals and nutrients obtained from other sources should be taken into account when prescribing / suggesting BIOGEN RAGE THERMO EXTREME.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

BIOGEN RAGE THERMO EXTREME is not indicated for use during pregnancy or lactation. Consult a health care provider prior to use if you are of childbearing age, pregnant or breastfeeding.

4.7 Effects on ability to drive and use machines

BIOGEN RAGE THERMO EXTREME is unlikely to affect the ability to drive a vehicle or use machines. Caution is advised not to drive a vehicle or operate machinery until the effects of BIOGEN RAGE THERMO EXTREME are known.

4.8 Undesirable effects

BIOGEN RAGE THERMO EXTREME is generally well tolerated.

Immune system disorders:

immune system usoruers:
Frequency unknown: hypersensitivity/allergy is known to occur, in which case, discontinue use. Caffeine can cause anaphylaxis in sensitive individuals, although true IgE-mediated caffeine allergy seems to be relatively rare. **Psychiatric disorders:** Frequency unknown: anxiety, agitation, irritability, mood changes.

Nervous system disorders: Frequency unknown: insomnia, nervousness, restlessness, tremors, convulsions, headache, sleep disturbances.

Ear and labyrinth disorders: Frequency unknown: ringing sound in the ears.

Cardiac disorders: Frequency unknown: tachycardia, chest pain, dysrhythmia

Respiratory, thoracic and mediastinal disorders: Frequency unknown: quickened respiration , tachypnea-induced respiratory alkalosis.

Gastrointestinal disorders: *Frequency unknown:* temporary gastric irritation, nausea, vomiting.

Renal and urinary disorders: Frequency unknown: diuresis.

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

See section 4.8. In the event of overdose, treatment should be symptomatic and supportive

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Grapefruit seed extract grapefruit flavonoids have demonstrated activity as catalysts of lipolysis, breaking down triglycerides stored in fat cells and stimulating the release of fatty acids and glycerol.

Guarana acts as a central nervous system (CNS) stimulant. Caffeine, the main constituent of guarana, increases resting energy expenditure (REE) and cellular thermogenesis. It also causes an increase in nonoxidative fatty acid turnover and lipid oxidation; however, the net effect on lipid oxidation is small. The effects of caffeine on energy expenditure and lipid metabolism seem to be mediated by both sympathetic and nonsympathetic mechanisms.

Citrus bioflavonoids are a source of antioxidants.

Caffeine anhydrous, increases resting energy expenditure (REE) or resting metabolic rate (RMR), and cellular

Yerba mate, contains caffeine. Caffeine increases resting energy expenditure (REE) and cellular thermogenesis. It also causes an increase in nonoxidative fatty acid turnover and lipid oxidation; however, the net effect on lipid oxidation is small.

Olive, leaf constituent, oleuropein, appears to have antioxidant activity.

L-theanine, Theanine is an amino acid which may promote weight loss effects.

 $\emph{Vitamin B}_{S_1}$ required in the acetylation reactions in gluconeogenesis; in the release of energy from carbohydrates; in the synthesis and degradation of fatty acids; and in the synthesis of sterols, steroid hormones, porphyrins, acetylcholine, and other compounds.

Black pepper/BioPerine: is a patented, standardised extract from black pepper containing 95% piperine (a bioavailability enhancer for nutrients). Used in combination with other ingredients it may enhance the uptake and utilisation of the natural actives increasing the bioavailability of supplemented nutrients through increased absorptio

Chromium potentiates the action of insulin and thus influences carbohydrate, fat and protein metabolism

Pharmacodynamic effects:

Grapefruit seed extract, Flavonoid-induced lipolysis occurs through inhibition of cAMP-phosphodiesterase and maintenance of lipolysis-inducing cAMP levels. Stimulation of adipose tissue lipolysis may upregulate the use of lipid energy by the body

Guarana, Caffeine is often used in combination with ephedra for weight loss and seems to have additive pharmacodynamic effects.

Citrus bioflavonoids, The flavonoid constituents naringin and nobiletin, found in sweet orange, might have anti-inflammatory activity

Caffeine anhydrous, The thermogenic effects of caffeine may be due to vasoconstriction and increase in vascular smooth muscle tone. Yerba mate, The effects of caffeine on energy expenditure and lipid metabolism seem to be mediated by both sympathetic and nonsympathetic mechanisms. Yerba mate may improve satiety, which might help reduce energy intake.

Olive, Phenolic compounds present in olive seem to possess antioxidant, vasodilating, and antiplatelet properties. The compounds act as free radical scavengers, inhibiting platelet aggregation and thromboxane release. Olive oil seems to increase low-density lipoprotein (LDL) cholesterol resistance to oxidation and therefore possibly decreases its contribution to atherogenesis.

e, L-theanine may act synergistically with caffeine and other constituents in green tea to cause weight loss

 $\it Vitamin~B_{S_7}$ Pantothenic acid is found in high levels in the brain when compared with the plasma, where it functions in normal biochemical pathways as the coenzyme, CoA. Acetyl-CoA, the precursor of acetylcholine, is derived from CoA. Black pepper/ BioPerine: As a thermo nutrient BioPerine® would potentially improve the process of nutrient absorption by enhancing thermogenesis. Most of the food or nutrient-induced thermogenesis is facilitated by beta receptors, which include a compound known as cyclic adenosine 3',5' monophosphate (cAMP). The role of cAMP as a "second messenger" to the hormonal and enzymatic actions in the body is well recognized. Piperine has been found in independent studies to stimulate the release of catecholamines, thermogenic hormones whose action is made possible by the presence of cAMP. Other mechanisms by which piperine stimulate nutrient absorption has also been discussed in literature. These include increased micelle formation, stimulation of active transport of amino acids (gamma-glutamyl transpeptidase), and epithelial cell wall modification due to the affinity of piperine towards fats and fatty substances.

Chromium, may induce these effects by affecting the brain's hunger receptors. Some research suggests that chromium might sensitize insulin-sensitive glucoreceptors in the brain, resulting in appetite suppression, activation of the sympathetic nervous system, stimulation of thermogenesis, and down-regulation of insulin secretion.

5.2 Pharmacokinetic properties

Absorption/Distribution/Metabolism/Excretion

Grapefruit seed extract,
There is insufficient reliable information available about the pharmacokinetics of grapefruit seed extract.

Guarana
There is insufficient reliable information available about the pharmacokinetics of guarana.

Citrus bioflavonoids,
There is insufficient reliable information available about the pharmacokinetics of citrus bioflavonoids.

Caffeine anhydrous,
Absorption: Caffeine is rapidly and almost completely (99%) absorbed from the gut after ingestion.
Peak levels in the circulation typically occur 30-60 minutes after ingestion. Distribution: Caffeine is widely distributed throughout the tissues of the body after oral, rectal, or parenteral administration. It crosses the blood-brain barrier, so effects are exerted both centrally and peripherally.

Metabolism: Caffeine is metabolized in the liver by cytochrome P450 1A2 (CYP1A2) enzymes to paraxanthine (84%), theophylline (4%), and theobromine (12%).

Excretion: The half-life of caffeine in healthy adults is 1.5-10 hours and is decreased by smoking

recovery within 8 hours.

Yerba mate,
Absorption: After oral consumption of yerba mate, the gastrointestinal absorption of certain polyphenol constituents, such as dihydrocaffeic, dihydroferulic, and dihydrocoumaric acids, can be delayed by colonic microbiota metabolism Distribution: High concentrations of caffeine and theobromine were found in the placenta, cord serum, neonatal urine, neonatal hair, meconium, and breast milk from a patient who reported drinking yerba mate during pregnancy.

Absorption: Following use of olive leaf extract, oleuropein and conjugated metabolites of hydroxytyrosol are found in the plasma

Metabolism: Following use of olive leaf extract, sulfated and glucuronidated metabolites of hydroxytyrosol and oleuropein are found in the plasma. Excretion: Following use of olive leaf extract, conjugated metabolites of hydroxytyrosol are found in the urine with

L-theanine,
Absorption: Theanine is absorbed through the intestines. The peak concentration of L-theanine in the plasma occurs at about 50 minutes after oral intake.

Distribution: Following absorption, L-theanine is distributed to the plasma and erythrocytes. L-theanine can cross the blood brain barrier and appears to do so in a dose-dependent manner.

Metabolism: L-theanine is hydrolyzed in the intestines to ethylamine and glutamic acid. Excretion: A small amount of L-theanine is retained in erythrocytes, but most L-theanine and its metabolites are excreted in the urine 3-24 hours after oral intake.

 $\mbox{\it Vitamin B}_{s_{7}}$ No clinical data are available for the metabolism and elimination of Vitamin Bs

Pantothenic acid is excreted in the urine.

Black pepper/BioPerine: There is insufficient reliable information available about the pharmacokinetics of black pepper. Chromium, Absorption: When ingested, most chromium is excreted unabsorbed in the feces.

Distribution: After absorption, chromium is bound to transferrin. The distribution may occur across fast, medium, and slow compartments, with serum chromium not in equilibrium with tissue-organ stores.

Excretion: The small percentage of chromium that is absorbed is rapidly excreted in the urine 6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aerosil Magnesium stearate Potato starch Vegetable capsule (containing hypromellose).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage Store at or below 25 °C. Protect from moisture. Keep in the original container until required for use

6.5 Nature and contents of container

Black PET container (250 mL) with a black Biogen PET lid. Packed in a unit carton. Pack size: 80 vegetable capsules

6.6 Special precautions for disposal and other handling No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biogen 23 Stag Road, Glen Austin, South Africa info@biogen.co.za

www.biogen.co.za Tel: 011 589 2322 8. REGISTRATION NUMBER

Will be allocated by SAHPRA upon registration. 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Will be allocated by SAHPRA upon registration.

JOB: BRS_Rage Thermo Extreme_80s **SIZE:** 210mm x 420 mm STOCK: Foil Substrate: Clear Substrate: White Substrate: Paper: X Other: **COLOURS:** FINISHING: Available Slot Slot Slot Foil / Holographic Foil Matte Gloss

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