PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE
RALOTRIN 60 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 60 mg raloxifene hydrochloride, equivalent to 56 mg raloxifene free base.
Excipient with known effect:
Each tablet contains sugar: lactose monohydrate 1,50 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet. White, elliptically tablets with dimensions: 12,6 mm± 0,1 mm; 6,6 mm± 0,1 and thickness 3,5 ± 0,2 mm.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
RALOTRIN is indicated for the prevention and treatment of osteoporosis in postmenopausal women.
Clinical studies have shown a reduction in the incidence of non-traumatic vertebral fractures. The effects of RALOTRIN on the risk for extra-vertebral fractures are not known. To reduce the risk of development of invasive breast cancer in postmenopausal women with osteoporosis.
The risk reduction is not applicable to oestrogen receptor negative (ER-) cancers and cancers of unknown oestrogen receptor status.

4.2 Posology and method of administration
Posology
The recommended dosage is one 60 mg RALOTRIN tablet daily by oral administration, which may be taken at any time of the day without regard to meals. Women receiving RALOTRIN should be given supplements of calcium if the daily intake is less than 800 mg per day.
Elderly:
No dose adjustment is necessary for the elderly.
Hepatic impairment:
RALOTRIN should not be used in patients with hepatic impairment (see section 4.3 and 4.4).
Renal impairment:
RALOTRIN should not be used in patients with severe renal impairment (see section 4.3).
Paediatric population:
RALOTRIN should not be used in children of any age. There is no relevant use of RALOTRIN in the paediatric population.
Method of administration
For oral use.

4.3 Contraindications
- Hypersensitivity to raloxifene or to any of the excipients of RALOTRIN listed in section 6.1.
- Pregnancy and lactation (see section 4.6).
- Active or past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
- Hepatic impairment including cholestasis and liver cirrhosis.
- Severe renal impairment.
- Unexplained uterine bleeding.
- RALOTRIN should not be used in patients with signs or symptoms of endometrial cancer as safety in this patient group has not been adequately studied.

4.4 Special warnings and precautions for use
Raloxifene, as in RALOTRIN is associated with an increased risk for venous thromboembolic events (see section 4.3). RALOTRIN should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness, or from 3 days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. In a study of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, raloxifene, as in RALOTRIN did not affect the incidence of myocardial infarction, hospitalized acute coronary syndrome, overall mortality, including overall cardiovascular mortality, or stroke, compared to placebo. However, there was an increase in death due to stroke in women assigned to raloxifene, as in RALOTRIN. The incidence of stroke mortality was 2,2 per 1000 women per year for raloxifene versus 1,5 per 1 000 women per year for placebo (see section 4.8). This finding should be considered when prescribing RALOTRIN for postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischemic attack or atrial fibrillation. There is no evidence of endometrial proliferation. Any uterine bleeding during RALOTRIN treatment is unexpected and should be fully investigated (see section 4.3). The two most frequent diagnoses associated with uterine bleeding during raloxifene, as in RALOTRIN, treatment were endometrial atrophy and benign endometrial polyps. The safety of RALOTRIN in patients with breast cancer or endometrial cancer has not been adequately studied. No data are available on the concomitant use of raloxifene, as in RALOTRIN, and medicines used in the treatment of early or advanced breast cancer. Therefore, RALOTRIN should be used for osteoporosis treatment and prevention only after the treatment of breast cancer, including adjuvant therapy, has been completed. Raloxifene is metabolised primarily in the liver. Single doses of raloxifene, as in RALOTRIN, given to patients with cirrhosis and mild hepatic impairment (Child-Pugh class A) produced plasma concentrations of raloxifene which were approximately 2,5 times the controls. The increase correlated with total bilirubin concentrations. Therefore RALOTRIN is not recommended to be used in patients with hepatic insufficiency (see section 4.3). Serum total bilirubin, gamma-glutamyl transferase, alkaline phosphatase, ALT and AST should be closely monitored during treatment with RALOTRIN if elevated values are observed. Limited clinical data suggest that in patients with a history of oral oestrogen-induced hypertriglyceridemia (>5,6 mmol/l), raloxifene, as in RALOTRIN, may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking raloxifene RALOTRIN. As safety information regarding co-administration of raloxifene as in RALOTRIN, with systemic oestrogens is limited, such use is not recommended. RALOTRIN is not effective in reducing vasodilatation (hot flushes), or other symptoms of the menopause associated with oestrogen deficiency. It should only be used in post-menopausal women (absence of periods for 12 months). Because of the indirect impact on serum testosterone levels and the potential ability for performance enhancement, raloxifene, as in RALOTRIN, is banned by the World Anti-doping Agency (WADA). RALOTRIN contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take RALOTRIN.

4.5 Interactions with other medicines and other forms of interaction
Raloxifene, as in RALOTRIN, should not be co-administered with cholestyramine (or other anion exchange resins), which significantly reduces the absorption and enterohepatic cycling of raloxifene. Concurrent administration of either calcium carbonate or aluminium and magnesium-hydroxide containing antacids do not affect the systemic exposure of raloxifene, as in RALOTRIN. Co-administration of raloxifene, as in RALOTRIN and warfarin does not alter the pharmacokinetics of either compound. However, modest decreases in the prothrombin time have been observed, and if RALOTRIN is given concurrently with warfarin or other coumarin derivatives, the prothrombin time should be monitored. Effects on prothrombin time may develop over several weeks if RALOTRIN treatment is started in patients who are already on coumarin anticoagulant therapy. Raloxifene has no effect on the pharmacokinetics of methylprednisolone given as a single dose. Raloxifene does not affect the steady-state AUC of digoxin. The Cmax of digoxin increased by less than 5 %. In clinical trials with raloxifene, as in RALOTRIN no interactions were noted with paracetamol, non-steroidal anti-inflammatory drugs (such as acetylsalicylic acid, ibuprofen, and naproxen), oral antibiotics, H1 antagonists, H2 antagonists, and benzodiazepines. No clinically relevant effects of the co-administration of the medicines on raloxifene plasma concentrations were identified. No interaction was noted with vaginal oestrogen preparations in clinical studies of raloxifene, as in RALOTRIN. Compared to placebo there was no increased use in raloxifene treated patients. Safety information regarding the concurrent use of RALOTRIN and systemic hormone therapy (oestrogen without progesterone) is limited. And therefore, concomitant use of RALOTRIN with systemic oestrogen is not recommended. In vitro, raloxifene did not interact with the binding of warfarin, phenytoin, or tamoxifen. Peak concentrations of raloxifene are reduced with co-administration with ampicillin. Since the overall extent of absorption and the elimination rate of raloxifene are not affected, RALOTRIN can be concurrently administered with ampicillin. Raloxifene modestly increases hormone-binding globulin concentrations, including sex steroid binding globulins (SHBG), thyroxine binding globulin (TBG), and corticosteroid binding globulin (CBG), with corresponding increases in total hormone concentrations. There is no evidence that these changes affect concentrations of the corresponding free hormones.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
RALOTRIN is only for use in postmenopausal women and must not be taken by women of childbearing potential. If RALOTRIN is used during pregnancy it may be associated with an increased risk of congenital defects in the foetus.

Pregnancy
RALOTRIN is contraindicated during pregnancy (see section 4.3).
RALOTRIN must not be taken by women of child-bearing potential. Raloxifene, as in RALOTRIN may cause foetal harm when administered to a pregnant woman. If this medicine is used mistakenly during pregnancy or the patient becomes pregnant while taking it, the patient should be informed of the potential hazard to the foetus (see section 5.3).

Breastfeeding
RALOTRIN is contraindicated during lactation (see section 4.3).
It is unknown whether RALOTRIN is excreted in human milk. A risk to newborns/infants cannot be excluded. Its clinical use, therefore, cannot be recommended in breastfeeding women. RALOTRIN may affect the development of the baby.

4.7 Effects on ability to drive and use machines
Raloxifene has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
a. Summary of the safety profile. The clinically most important adverse reactions reported in postmenopausal women treated with RALOTRIN were venous thromboembolic events (see section 4.4).

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Nervous system disorders	Frequent	Headache, including migraine
	Less frequent	Fatal strokes
Vascular disorders	Frequent	Vasodilation (hot flushes)
	Less frequent	Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, superficial vein thrombophlebitis, Arterial thromboembolic reactions
Gastrointestinal disorders	Frequent	Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, dyspepsia
Hepato-biliary disorders	Frequent	Cholelithiasis
Skin and subcutaneous tissue disorders	Frequent	Rash
Musculoskeletal and connective tissue disorders	Frequent	Leg cramps
Reproductive system and breast disorders	Frequent	Breast symptoms such as pain, enlargement and tenderness
General disorders and administration site conditions	Frequent	Flu syndrome, Peripheral oedema
Investigations	Frequent	Increased blood pressure
	Frequency unknown	Increase in serum triglycerides, increases in AST and/or ALT, decrease in serum fibrinogen.

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. 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 some clinical trials, daily doses were given up to 600 mg for 8 weeks and 120 mg, for 3 years. No cases of raloxifene overdose were reported during clinical trials. In adults, symptoms of leg cramps and dizziness have been reported in patients who took more than 120 mg as a single ingestion. In some cases, no adverse events were reported as a result of the overdose. In accidental overdose in children younger than 2 years of age, the maximum reported dose has been 180 mg. In children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhoea, tremor, and flushing, and elevation in alkaline phosphatase. There is no specific antidote for RALOTRIN. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A 21.13 Others
Pharmacotherapeutic group: Selective Oestrogen Receptor Modulator, ATC code: G03XC01.
Raloxifene is a non-steroidal benzothiophene derivative which acts as a Selective Oestrogen Receptor Modulator (SERM). The selective profile of raloxifene includes oestrogen agonist effects on bone and lipids and oestrogen antagonist effects in breast and uterine tissues.
Skeletal effects: Raloxifene reduces the resorption of bone and decreases overall bone turnover. In clinical trials in women who were 2 to 8 years postmenopausal, raloxifene 60 mg per day produced significant increases in bone mineral density (BMD) of hip and spine as well as total body mineral mass compared to placebo. Bone quality was maintained during these trials. Treatment with raloxifene for three years in postmenopausal women with a mean age of 66 years and with osteoporosis reduced the incidence of vertebral fractures.
Effects on lipid metabolism: In clinical trials, raloxifene decreased serum total cholesterol and LDL cholesterol without significant effects on serum total HDL cholesterol or triglycerides. Raloxifene increased serum HDL-2 cholesterol and apolipoprotein A1, while serum fibrinogen, apolipoprotein B and lipoprotein(a) were decreased.
Effects on the endometrium: Raloxifene was not associated with endometrial thickening (see section 4.4).
Effects on breast tissue: Raloxifene has no stimulatory effect on breast tissue. Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast symptoms.
A reduction in the risk to develop invasive breast cancer has been reported in postmenopausal women with osteoporosis who were treated with raloxifene.
The reduction in the risk to develop breast cancer is not applicable to oestrogen receptor negative (ER-) cancers and cancers of unknown oestrogen receptor status.

5.2 Pharmacokinetic properties
Absorption: Approximately 60 % of an oral dose is absorbed. Pre-systemic glucuronidation is extensive. Absolute bioavailability of raloxifene is 2 %.
Distribution: Raloxifene is distributed extensively in the body. The volume of distribution is not dose-dependent.
Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins, including both albumin and a-1-acid-glycoprotein.
Metabolism: Raloxifene undergoes extensive first pass metabolism to glucuronide conjugates. Raloxifene levels are maintained by enterohepatic recycling, giving a plasma half-life of 27,7 hours.
Excretion: The majority of a dose of raloxifene and glucuronide metabolites are excreted within 5 days and are found primarily in the faeces, with less than 6 % excreted in the urine.
Special populations:
Renal insufficiency: See ‘Excretion’ above.
Hepatic insufficiency: Raloxifene is metabolised primarily in the liver. Safety and efficacy of raloxifene has not been studied in patients with impaired liver function. Raloxifene was studied as a single dose in patients with Child-Pugh Class A cirrhosis with a total serum bilirubin ranging from 10,3 to 34,2 µmol/L. Plasma concentrations were approximately 2,5 times higher than in controls and correlated with total bilirubin concentrations.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium starch glycolate, Citric acid monohydrate, Microcrystalline cellulose, Dibasic calcium phosphate, Poloxamer 407, Magnesium stearate, Titanium dioxide (E171), Lactose monohydrate, Hypromellose (E464) and Macrogol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 25 °C.

6.5 Nature and contents of container
RALOTRIN is packed in transparent PVC/PE/PVDC blister with aluminium foil. The blister strips are packed in cartons.
Pack sizes:
7, 14, 28 and 30 film coated tablets.
Not all packs and pack sizes may be marketed.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd. 106, 16th Road, Midrand, 1686, South Africa.

8. REGISTRATION NUMBER(S)
RALOTRIN: 49/21.13/0672

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24 July 2022

10. DATE OF REVISION OF THE TEXT
N.A

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS: S3

1. NAAM VAN DIE MEDISYNE
RALOTRIN 60 mg filmbedekte tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke filmbedekte tablet bevat 60 mg raloksifeenhidrochloried, gelykstaande aan 56 mg raloksifeen vrye basis.
Hulpstof met bekende effek:
Elke tablet bevat suiker: laktosemonohidraat 1,50 mg. Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM
Filmbedekte tablet. Wit, elliptiese tablette met demensies: 12,6 mm± 0,1 mm, 6,6 mm± 0,1 en dikte 3,5 ± 0,2 mm.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
RALOTRIN word aangedui vir die voorkoming van osteoporose in postmenopousale vroue. Kliniese studies het 'n verminderde insidensie van nie-traumatiese vertebrale frakture aangetoon. Die effekte van RALOTRIN op die risiko vir ekstra-vertebrale frakture is nie bekend nie. Om die risiko van indringende borskanker te verminder by postmenopousale vroue met osteoporose. Die risikovermindering is nie van toepassing op estrogeenreseptor-negatiewe (ER-) kankers en kankers van onbekende estrogeenreseptorstatus nie.

4.2 Posologie en metode van toediening
Posologie
Die aanbevole dosis is een 60 mg RALOTRIN tablet daagliks met orale toediening, wat enige tyd van die dag geneem mag word sonder inagneming van maaltye. Vroue wat RALOTRIN ontvang, moet kalsiumaanvullings ontvang indien die daaglikse inname minder is as 800 mg per dag.
Bejaardes:
Geen dosisaanpassing by bejaardes is nodig nie.
Hepatiese inkorting:
RALOTRIN moet nie by pasiënte met hepatiese inkorting gebruik word nie (sien afdeling 4.3 en 4.4).
Renale inkorting:
RALOTRIN moet nie by pasiënte met erge renale inkorting gebruik word nie (sien afdeling 4.3).
Pediatriese populasie:
RALOTRIN moet nie by kinders van enige ouderdom gebruik word nie. Daar is geen relevante gebruik van RALOTRIN in die pediatriese populasie nie.
Metode van toediening
Vir orale gebruik.

4.3 Kontraïndikasies
- Hipersensitiwiteit teenoor raloksifeen of enige van die hulpstowwe van RALOTRIN gelys in afdeling 6.1.
- Swangerskap en laktasie (sien afdeling 4.6)
- Aktiewe- of geskiedenis van vorige veneuse tromboëmboliese insidente (VTI), insluitend diepvenatrombose, pulmonêre embolisme en trombose van die retinale vene.
- Hepatiese inkorting, insluitend cholestase en lewersirrose.
- Erge renale inkorting.
- Onverklaarbare uteriene bloeding.
- RALOTRIN moet nie by pasiënte met tekens of simptome van endometriële kanker gebruik word nie, aangesien die veiligheid in hierdie pasiënt groep nie voldoende bestudeer is nie.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Raloksifeen, soos in RALOTRIN word geassosieer met 'n verhoogde risiko van tromboëmboliese insidente (sien afdeling 4.3). RALOTRIN moet gestaak word in geval van siekte of 'n toestand wat lei tot 'n verlengde periode van immobilisering. Staking moet plaasvind so gou as moontlik tydens siekte, of 3 dae voor immobilisasie begin. Behandeling moet nie hervat word totdat die inisiërende toestand opgeklaar het en die pasiënt weer volledig mobiel is nie. In 'n studie van postmenopousale vroue met gedokumenteerde koronêre hartsiektes of 'n verhoogde risiko van koronêre insidente, het raloksifeen, soos in RALOTRIN, nie die voorkoms beïnvloed van miokardiale infarksie, gehospitaliseerde akute koronêre sindroom, algehele mortaliteit, insluitend algehele kardiovaskulêre mortaliteit, of beroerte, in vergelyking met placebo, nie. Daar was egter 'n toename in die sterftes as gevolg van beroerte by vroue wat aan raloksifeen, soos in RALOTRIN, geallokeer was. Die insidensie van beroerte mortaliteit was 2,2 per 1 000 vroue per jaar vir raloksifeen teenoor 1,5 per 1 000 vroue per jaar vir placebo (sien afdeling 4.8). Hierdie bevinding moet oorweeg word wanneer RALOTRIN voorgeskryf word by postmenopousale vroue met 'n geskiedenis van beroerte of ander beduidende beroerte-risikofaktore, soos kortstondige iskemiese aanval of atriale fibrillasie. Daar is geen bewyse van endometriële proliferasie nie. Enige uteriene bloeding tydens RALOTRIN behandeling is onverwags en moet ten volle ondersoek word (sien afdeling 4.3). Die twee mees algemeenste diagnoses wat geassosieer word met uteriene bloeding tydens raloksifeen, soos in RALOTRIN, behandeling is endometriële atrofie en benigne endometriële poliepe. Die veiligheid van RALOTRIN by pasiënte met borskanker of endometriële kanker is nie voldoende bestudeer nie. Geen data is beskikbaar oor die gesamentlike gebruik van raloksifeen, soos in RALOTRIN, en medisyne wat gebruik word vir die behandeling van vroeë of gevorderde borskanker nie. Dus, RALOTRIN moet gebruik word vir osteoporose-behandeling en -voorkoming slegs nadat die behandeling van borskanker, insluitend aanvullende terapie, voltooi is. Raloksifeen word hoofsaaklik in die lewer gemetaboliseer. Enkel dosisse raloksifeen, soos in RALOTRIN, gegee aan pasiënte met sirrose en ligte hepatiese inkorting (Child-Pugh klas A) het plasmakonsentrasies van raloksifeen geproduseer wat ongeveer 2,5 keer di**é van die** kontroles was. Die toename het gekorreleer met totale bilirubienkonsentrasies. Daarom word RALOTRIN nie aanbeveel om gebruik te word by pasiënte met hepatiese ontoereikendheid nie (sien afdeling 4.3). Serum totale bilirubien, gammaglutamieltransferase, alkalienfosfatase, ALT en AST moet noukeurig gemonitor word tydens behandeling met RALOTRIN indien verhoogde waardes waargeneem word. Beperkte kliniese data stel voor dat by pasiënte met 'n geskiedenis van orale estrogeen- geïnduseerde hipertrigliseriedemie (>5,6 mmol/l), raloksifeen, soos in RALOTRIN, geassosieer kan word met 'n duidelike toename in serum trigliseriede. Pasiënte met hierdie mediese geskiedenis se serum trigliseriede moet gemonitor word wanneer raloksifeen, RALOTRIN geneem word. Aangesien veiligheidsinligting rakende die gesamentlike toediening van raloksifeen, soos in RALOTRIN, met sistemiese estrogene beperk is, word sodanige gebruik nie aanbeveel nie. RALOTRIN is nie effektief in die vermindering van vasodilatasie (warm gloede) of ander simptome van menopouse wat geassosieer word met estrogeentekort nie. Dit moet slegs gebruik word in postmenopousale vroue (afwesigheid van maandstondes vir 12 maande). Vanweë die indirekte impak op serum testosteroonvlakke en die potensiële vermoë om 'n mens beter te laat presteer, word raloksifeen, soos in RALOTRIN, deur die Wêreld Anti Dwelm Agentskap (WADA) verbied. RALOTRIN bevat laktose. Pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, die Lapp-laktase tekort of glukose-galaktose wanabsorpsie moet nie RALOTRIN neem nie.

4.5 Interaksie met ander medisyne en ander vorme van interaksie
Raloksifeen, soos in RALOTRIN, moet nie saam met cholestiramien (of ander anioon-uitruilingsharse), wat die opname en enterohepatiese sirkulasie van raloksifeen aansienlik verminder, toegedien word nie. Gelyktydige toediening van kalsiumkarbonaat- of aluminium- en magnesiumhidroksied-bevattende teensuurmiddels, beïnvloed nie die sistemiese blootstelling van raloksifeen, soos in RALOTRIN, nie. Gesamentlike toediening van raloksifeen, soos in RALOTRIN en warfarien verander nie die farmakokinetika van enigeen van die samestellings nie. Daar is egter matige afnames in die protrombientyd waargeneem, en indien RALOTRIN gelyktydig met warfarien of ander kumarienderivate gegee word, moet die protrombientyd gemonitor word. Effekte op protrombientyd kan oor 'n paar weke ontwikkel indien RALOTRIN behandeling begin word by pasiënte wat reeds op kumarien-antikoagulantterapie is. Raloksifeen het geen effek op die farmakokinetika van metielprednisoloon wat as 'n enkele dosis gegee word nie. Raloksifeen beïnvloed nie die gelykvlak AOK van digoksien nie. Die K_{maks} van digoksien het met minder as 5 % gestyg. In kliniese proewe met raloksifeen, soos in RALOTRIN was daar geen interaksies waargeneem met parasetamol, nie-steroïdale anti-inflammatoriese middels (soos asetielsalisielsuur, ibuprofeen en naprokseen), orale antibiotika, H1 antagoniste, H2 antagoniste en bensodiasepiene nie. Geen klinies relevante effekte van die gelyke toediening van hierdie medisyne op die plasmakonsentrasies van raloksifeen was geïdentifiseer nie. Geen interaksie was opgemerk met vaginale estrogeenpreparate in kliniese studies van raloksifeen, soos in RALOTRIN, nie. In vergelyking met placebo, was daar geen toenemende gebruik by pasiënte wat met raloksifeen behandel was nie. Veiligheidsinligting rakende die gelyktydige gebruik van RALOTRIN en sistemiese hormoonterapie (estrogeen sonder progesteroon) is beperk. En daarom word gelyktydige gebruik van RALOTRIN met sistemiese estrogeen nie aanbeveel nie. *In vitro* het raloksifeen geen interaksie met die binding van warfarien, fenitoïen of tamokifeen gehad nie. Piekkonsentrasies van raloksifeen word verminder met die gesamentlike toediening van ampisillien. Aangesien die algehele omvang van absorpsie en die eliminasietempo van raloksifeen nie beïnvloed word nie, kan RALOTRIN gelyktydig met ampisillien toegedien word. Raloksifeen verhoog matiglik, die hormoon-bindende globulienkonsentrasies, insluitend seks steroïed-bindende globuliene (SHBG), tiroksien-bindende globulien (TBG), en kortikosteroïed-bindende globulien (CBG), met ooreenstemmende toenames in totale hormoonkonsentrasies. Daar is geen bewyse dat hierdie veranderinge die konsentrasies van die ooreenstemmende vrye hormone beïnvloed nie.

4.6 Vrugbaarheid, swangerskap en laktasie
Vroue van kinderbarende potensiaal
RALOTRIN is slegs vir die gebruik by postmenopousale vroue en moet nie deur vroue van kinderbarende potensiaal geneem word nie. Indien RALOTRIN tydens swangerskap gebruik word, kan dit geassosieer word met 'n verhoogde risiko van kongenitale defekte in die fetus.

Swangerskap
RALOTRIN is gekontraïndikeerd tydens swangerskap (sien afdeling 4.3). RALOTRIN moet nie deur vroue van kinderbarende potensiaal geneem word nie. Raloksifeen, soos in RALOTRIN, kan fetale skade veroorsaak indien dit aan 'n swanger vrou toegedien word. Indien hierdie medisyne verkeerdelik tydens swangerskap gebruik word, ó**f die pasiënt swanger raak tydens die gebruik daarvan, moet die pasiënt ingelig word oor die moontlike gevaar vir die fetus (sien afdeling 5.3).**

Borsvoeding
RALOTRIN is gekontraïndikeerd tydens laktasie (sien afdeling 4.3). Dit is nie bekend of RALOTRIN in menslike melk uitgeskei word nie. 'n Risiko vir pasgeborenes/suigelinge kan nie uitgesluit word nie. Die kliniese gebruik daarvan kan dus nie aanbeveel word by borsvoedende vroue nie. RALOTRIN kan die ontwikkeling van die baba beïnvloed.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik
Raloksifeen het geen of 'n weglaatbare klein invloed op die vermoë om te bestuur en masjinerie te gebruik.

3.8 Newe-effekte
a. Opsomming van die veiligheidsprofiel
Die klinies belangrikste newe-effekte wat aangemeld is by postmenopousale vroue wat met RALOTRIN behandel was, is veneuse tromboëmboliese insidente (sien afdeling 4.4).
b. Getabuleerde opsomming van newe-effekte

Sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Bloed- en die limfstelselversteurings	Minder gereeld	Trombositopenie
Senusisteemversteurings	Gereeld	Hoofpyn, insluitend migraine
	Minder gereeld	Fatale beroertes
Vaskulêre versteurings	Gereeld	Vasodilatasie (warm gloede)
	Minder gereeld	Veneuse tromboëmboliese insidente, insluitend diepvenatrombose, pulmonêre embolisme, trombose van die retinale vene, oppervlakkige tromboflebitis van die vene, arteriële tromboëmboliese reaksies
Gastroïntestinale versteurings	Gereeld	Gastroïntestinale simptome soos naarheid, abdominale pyn, dispepsie
Hepato-bilière versteurings	Gereeld	Cholelitiase
Vel- en Onderhuidse weefselversteurings	Gereeld	Uitslag
Muskuloskeletale bindweefselversteurings	Gereeld	Beenkrampe
Voorplantingstelsel- en borsversteurings	Gereeld	Borssimptome soos pyn, vergroting en teerheid
Algemene versteurings en toedieningsplektoestande	Gereeld	Griepsindroom, Perifere edeem
Ondersoeke	Gereeld	Verhoogde bloeddruk
	Frekwensie onbekend	Toename in serumtrigliseriede, toename in AST en/of ALT, afname in serumfibrinogeen.

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgdeskundiges word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reactions Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word:
https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
In sommige kliniese proewe, is daaglikse dosisse van tot en met 600 mg vir 8 weke en 120 mg vir 3 jaar gegee. Geen gevalle van raloksifeen oordosering is tydens kliniese proewe aangemeld nie. By volwassenes is simptome van beenkrampe en duiseligheid gerapporteer by pasiënte wat meer as 120 mg as 'n enkele inname geneem het. In sommige gevalle is geen newe-effekte, as gevolg van die oordosis, aangemeld nie. In toevallige oordosering by kinders jonger as 2 jarige ouderdom, was die maksimum aangemelde dosis 180 mg. By kinders, het aangemelde simptome ataksie, duiseligheid, braking, uitslag, diarree, tremor en warm gloede asook verhogings in alkaliese fosfatase ingesluit. Daar is geen spesifieke teenmiddel vir RALOTRIN nie. Behandeling is simptomaties en ondersteunend.

5. FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
Kategorie en klas: A 21.13 Ander
Farmakoterapeutiese groep: Selektiewe Estrogeenreseptor-Moduleerder, ATK-kode: G03XC01. Raloksifeen is 'n nie-steroïedale bensotiofeen derivaat wat dien as 'n selektiewe estrogeenreseptor-moduleerder (SERM). Die selektiewe profiel van raloksifeen sluit in estrogeen-agonistiese effekte op been en lipiede asook estrogeen-antagonistiese effekte op weefsel van die bors en uterus.
***Skeletale effekte*:** Raloksifeen verminder die resorpsie van been en verminder die algehele beenomset. In kliniese proewe by vroue wat 2 tot 8 jaar postmenopousaal was, het raloksifeen 60 mg per dag aansienlike toenames in beenmineraaldigtheid (BMD) van die heup en spina gelewer, asook totale liggaamsmineraalmassa in vergelyking met placebo. Beengehalte is tydens hierdie proewe gehandhaaf. Behandeling met raloksifeen vir drie jaar by postmenopousale vroue met 'n gemiddelde ouderdom van 66 jaar en met osteoporose het die voorkoms van vertebrale frakture verminder.
Effekte op lipiedmetabolisme: In kliniese proewe het raloksifeen die totale serum cholesterol en LDL-cholesterol verminder sonder beduidende effekte op die totale serum HDL-cholesterol of trigliseriede. Raloksifeen verhoog serum HDL-2 cholesterol en apolipoproteïen A1, terwyl serumfibrinogeen, apolipoproteïen B en lipoproteïen(a) verminder het.
Effekte op die endometrium: Raloksifeen is nie geassosieer met endometriale verdikking nie (sien afdeling 4.4).
Effekte op borsweefsel: Raloksifeen het geen stimulerende effek op borsweefsel nie. Regoor alle placebo-beheerde proewe, was raloksifeen onderskeibaar van placebo met betrekking tot frekwensie en erns van borssimptome. 'n Verminderde risiko om indringende borskanker te ontwikkel, is by postmenopousale vroue met osteoporose aangemeld, wat met raloksifeen behandel is. Die verminderde risiko om borskanker te ontwikkel is nie van toepassing op estrogeenreseptor negatiewe (ER-) kankers en kankers met 'n onbekende estrogeenreseptorstatus nie.

5.2 Farmakokinetiese eienskappe
Absorpsie: Ongeveer 60 % van 'n orale dosis word geabsorbeer. Pre-sistemiese glukuronidasie is ekstensief. Absolute biobeskikbaarheid van raloksifeen is 2 %.
Verspreiding: Raloksifeen word breedvoerig in die liggaam versprei. Die verspreidingsvolume is nie dosisafhanklik nie. Raloksifeen en die monoglukuroniedkonjugate is hoogs gebonde aan plasmaproteïene, insluitend beide albumien en a-1-suur glikoproteïen.
Biotransformasie: Raloksifeen ondergaan ekstensiewe eerstedeurgangsmetabolisme na glukuroniedkonjugate. Raloksifeenvlakke word gehandhaaf deur enterohepatiese herwinning, met 'n plasma halfleeftyd van 27,7 uur.
Eliminasie: Die grootste hoeveelheid van 'n dosis raloksifeen en glukuroniedmetaboliete word binne 5 dae uitgeskei en word hoofsaaklik in die feses gevind, met minder as 6 % wat uitgeskei word in die urine.
Spesiale populasies:
Renale ontoereikendheid: Sien 'Eliminasie' hierbo.
Hepatiese ontoereikendheid:
Raloksifeen word hoofsaaklik in die lewer gemetaboliseer. Veiligheid en effektiwiteit van raloksifeen is nie bestudeer by pasiënte met 'n ingekorte lewerfunksie nie. Raloksifeen is as 'n enkele dosis bestudeer by pasiënte met Child-Pugh Klas A sirrose met 'n totale serumbilirubien wat wissel van 10,3 tot 34,2 µmol/L. Plasmakonsentrasies was ongeveer 2,5 keer hoër as in kontroles en het gekorreleer met totale bilirubienkonsentrasies.

6 FARMSEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Natriumstyselglikolaat, Sitroensuurmonohidraat, Mikrokristallien sellulose, Dibasiese kalsiumfosfaat, Poloksameer 407, Magnesiumstearaat, Titanium dioksied (E171), Laktosemonohidraat, Hipromellose (E464) en Makrogol.

6.2 Onverenigbaarheid
Nie van toepassing nie.

6.3 Rakleeftyd
36 maande.

6.4 Spesiale voorsorgmaatreëls tydens berging
Stoor benede 25 °C.

6.5 Aard en inhoud van die houer
RALOTRIN word verpak in deursigtige PVC/PE/PVDC stulpverpakking met aluminiumfoelie. Die stulpstroke word in kartonne verpak.
Verpakkingsgroottes:
7, 14 en 28 filmbedekte tablette. Nie alle verpakkings en verpakkingsgroottes mag moontlik bemark word nie.

6.6 Spesiale voorsorgmaatreëls vir die wegdoen en ander hantering van die produk
Geen spesiale vereistes.

7. HOUER VAN REGISTRASIESERTIFIKAAT
Trinity Pharma (Edms.) Bpk. 106, 16de Weg, Midrand, 1686, Suid Afrika.

8. REGISTRASIENOMMER(S)
RALOTRIN: 49/21.13/0672

9. DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
24 Julie 2022

10. DATUM VAN HERSIENING VAN DIE TEKS
N.A