PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE
NOCTRIN 2 mg (Prolonged Release Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged release tablet contains 2 mg melatonin.

Excipient with known effect:
Contains 90,00 mg of lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged Release Tablets.
White to off-white, round, biconvex shaped tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
NOCTRIN 2 mg is indicated for the short term (3 weeks) treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over.

4.2 Posology and method of administration
Posology
The recommended dose in patients 55 years and older is 2 mg once daily, 1 - 2 hours before bedtime and after food. The dosage may be continued for 3 weeks. Efficacy in patients younger than 55 years has not been demonstrated.

Paediatric use
NOCTRIN 2 mg is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

Renal insufficiency
The effect of any stage of renal insufficiency on melatonin pharmacokinetics has not been studied.

Hepatic impairment
There is no experience with NOCTRIN 2 mg in patients with liver impairment. Data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, NOCTRIN 2 mg is not recommended for use in patients with hepatic impairment.

Method of administration
For oral use.
Tablets should be swallowed whole to maintain prolonged release properties. The tablet should not be crushed or chewed to facilitate swallowing. Tablets should be taken after a meal.

4.3 Contraindications
Hypersensitivity to melatonin or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Autoimmune disease
No clinical data exist concerning the use of NOCTRIN 2 mg in individuals with autoimmune diseases. Therefore, NOCTRIN 2 mg is not recommended for use in patients with autoimmune diseases.

Excipients
NOCTRIN 2 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take NOCTRIN 2 mg.

Paediatric population
NOCTRIN 2 mg is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

4.5 Interaction with other medicines and other forms of interaction
Interaction studies have only been performed in adults.

Pharmacokinetic interactions
- Melatonin has been observed to induce CYP3A *in vitro* at supra-therapeutic concentrations. The clinical relevance of this finding is unknown. If induction occurs, this can give rise to reduced plasma concentrations of concomitantly administered medicines.
- Melatonin does not induce CYP1A enzymes *in vitro* at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.
- Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and a 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C19. The combination should be avoided.
- Caution should be exercised in patients on 5- or 8-methoxypsoralen (5-MOP and 8-MOP), which increases melatonin levels, by inhibiting its metabolism.
- Caution should be exercised in patients on cimetidine, a CYP2D inhibitor, which increases melatonin levels by inhibiting its metabolism.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.
- Caution should be exercised in patients on oestrogens (e.g., contraceptives or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.
- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
- There is a large amount of data available in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of NOCTRIN 2 mg or *vice versa* has not been studied.
- Alcohol should not be taken with NOCTRIN 2 mg, because it reduces the effectiveness of NOCTRIN 2 mg on sleep.
- NOCTRIN 2 mg may enhance the sedative properties of benzodiazepines and nonbenzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.
- NOCTRIN 2 mg has been co-administered in studies with thioridazine and imipramine. No clinically significant pharmacokinetic interactions were found. However, melatonin co-administration resulted in increased feelings of tranquillity and difficulty in performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone.

4.6 Fertility, pregnancy and lactation
Pregnancy
Safety in pregnancy and lactation has not been established. There are no clinical data available on use in pregnancy. In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Breastfeeding
Endogenous melatonin was measured in breast milk, thus exogenous melatonin is probably secreted into human milk. Therefore, breastfeeding is not recommended in women under treatment with melatonin.

4.7 Effects on ability to drive and use machines
Melatonin may cause drowsiness. Patients should avoid engaging in hazardous activities (such as driving or operating machinery) after taking NOCTRIN 2 mg (see section 4.8).

4.8 Undesirable effects
The following adverse reactions were reported in clinical trials and from post-marketing spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Less frequent*	Herpes zoster
Blood and lymphatic disorders	*Less frequent*	Leukopenia Thrombocytopenia
Immune system disorders	*Frequency unknown*	Hypersensitivity reaction
Metabolism and nutrition disorders	*Less frequent*	Hypertriglyceridaemia Hypocalcaemia Hyponatraemia
Psychiatric disorders	*Less frequent*	Irritability Nervousness Restlessness Insomnia Abnormal dreams Nightmares Anxiety Altered mood Aggression Agitation Crying Stress symptoms Disorientation Early morning awakening Increased libido Depressed mood Depression
Nervous system disorders	*Less frequent*	Migraine Headache Lethargy Psychomotor Hyperactivity Dizziness Somnolence Syncope Memory impairment Disturbance in attention Dreamy state Restless legs Poor quality sleep Paraesthesia
Eye disorders	*Less frequent*	Reduced visual acuity Blurred vision Increased lacrimation
Ear and labyrinth disorders	*Less frequent*	Positional vertigo Vertigo
Cardiac disorders	*Less frequent*	Angina pectoris Palpitations
Vascular disorders	*Less frequent*	Hypertension Hot flushes
Gastrointestinal disorders	*Less frequent*	Abdominal pain (upper) Abdominal discomfort Gastritis Dyspepsia Mouth ulceration Nausea Constipation Dry mouth Gastrointestinal upset Gastro-oesophageal reflux Oral mucosal blistering Tongue ulceration Vomiting Abnormal bowel sounds Flatulence Salivary hypersecretion Halitosis
Hepatobiliary disorders	*Less frequent*	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	*Less frequent*	Dermatitis Night sweats Hyperhidrosis Eczema Erythema Pruritic rash Pruritus Dry skin Nail disorder Night sweats Hand dermatitis Psoriasis
	Frequency unknown	Angioedema Oedema of mouth Tongue oedema
Musculoskeletal and connective tissue disorders	*Less frequent*	Pain in extremities Arthritis Muscle cramp Neck pain Night cramps
Renal and urinary disorders	*Less frequent*	Glycosuria Proteinuria Polyuria Haematuria Nocturia
Reproductive system and breast disorders	*Less frequent*	Menopausal symptoms Priapism Prostatitis
	Frequency unknown	Galactorrhoea
General disorders and administration site conditions	*Less frequent*	Asthenia Chest pain Fatigue Pain Thirst
Investigations	*Less frequent*	Increased weight Abnormal liver test Hepatic enzyme increase Abnormal blood electrolyte Abnormal laboratory tests

b. 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
No case of overdosage has been reported. If overdosage occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 2.2 Sedatives, Hypnotics.
Pharmacotherapeutic Group: Psycholeptics, Melatonin Receptor Agonists.
ATC Code: N05CH01.

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. The activity of melatonin at the melatonin 1 (MT1), melatonin 2 (MT2) and melatonin 3 (MT3) receptors is believed to contribute to its sleep promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

5.2 Pharmacokinetic properties
Absorption
The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50 % in the elderly. The kinetics of melatonin is linear over the range of 2 - 8 mg.

Bioavailability is in the order of 15 %. There is a significant first pass effect with an estimated first pass metabolism of 85 %. T_{max} occurs after 3 hours in a fed state. The rate of melatonin absorption and C_{max} following oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max} = 3,0 h versus T_{max} = 0,75 h) and lower peak plasma concentration in the fed state (C_{max} = 1020 pg/mL versus C_{max} = 1176 pg/mL).

Distribution
The *in vitro* plasma protein binding of melatonin is approximately 60 %. Melatonin is mainly bound to albumin, alpha1-acid glycoprotein and high-density lipoprotein.

Biotransformation
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite, 6-sulphatoxy-melatonin (6-S-MT), is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination
Terminal half-life ($t_{½}$) is 3,5 - 4 hours. Elimination is by renal excretion of metabolites, 89 % as sulphated and glucuronide conjugates of 6-hydroxymelatonin and 2 % is excreted as unchanged melatonin.

Gender
A 3- to 4-fold increase in C_{max} is apparent for women compared to men. A five-fold variability in C_{max} between different members of the same gender has also been observed. No pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations
Elderly
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older subjects compared to younger subjects, reflecting lower metabolism of melatonin in the elderly. C_{max} levels around 500 pg/mL in adults (18 - 45) versus 1200 pg/mL in the elderly (55 - 69); AUC levels around 3000 pg/h/mL in adults versus 5000 pg/h/mL in the elderly.

Renal impairment
There is no accumulation after repeated dosing. This finding is compatible with the short half-life in humans. The levels assessed in the blood of patients with end stage renal disease on chronic haemodialysis, at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411,4 ± 56,5 and 432,0 ± 83,2 pg/mL respectively and are similar to those found in healthy volunteers following a single dose of 2 mg melatonin.

Hepatic impairment
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels. Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Calcium hydrogen phosphate dehydrate
Ammonio methacrylate copolymer (Type B)
Purified talc
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities
Unknown.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store at or below 25 ºC.
Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container
Tablets are packed in PVC/PVDC/Al or Alu/Alu blister packs of 21, 30 or 7 tablets.
The blisters are then packed in cardboard boxes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

8 REGISTRATION NUMBER(S)
NOCTRIN XR 2 MG: 52/2.2/0780

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
24 May 2022

10 DATE OF REVISION OF THE TEXT
N.A

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PROFESSIONELE INLIGTING

SKEDULERINGSTATUS

S4

1 NAAM VAN DIE MEDISYNE
NOCTRIN 2 mg (Verlengde-vrystellingstablette)

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke verlengde-vrystellingstablet bevat 2 mg melatonien.

Hulpstowwe met bekende effek:
Bevat 90,00 mg laktosemonohidraat per tablet.

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3 FARMASEUTIESE VORM
Verlengde-vrystellingstablette.
Wit tot naaswit, ronde, bikonveks gevormde tablette.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
NOCTRIN 2 mg word aangedui vir die korttermyn (3 weke) behandeling van primêre slaaploosheid gekenmerk deur swak kwaliteit slaap by pasiënte wat 55 jaar of ouer is.

4.2 Posologie en metode van toediening
Posologie
Die aanbevole dosis by pasiënte van 55 jaar en ouer is 2 mg een maal per dag, 1 - 2 uur voor slapenstyd en na voedsel. Die dosis mag vir 3 weke voortgesit word. Effektiwiteit by pasiënte jonger as 55 jaar is nie vasgestel nie.

Pediatriese gebruik
NOCTRIN 2 mg word nie aanbeveel vir gebruik by kinders en adolessente onder die ouderdom van 18 nie as gevolg van onvoldoende data oor die veiligheid en effektiwiteit.

Renale ontoereikendheid
Die effek van enige stadium van renale ontoereikendheid op die farmakokinetika van melatonien is nie bestudeer nie.

Hepatiese inkorting
Daar is geen ervaring met NOCTRIN 2 mg by pasiënte met lewerinkorting nie. Data toon merkwaardig verhoogde endogene melatonienvlakke gedurende dagure as gevolg van verminderde opruiming by pasiënte met hepatiese inkorting. Daarom word NOCTRIN 2 mg nie aanbeveel vir gebruik by pasiënte met hepatiese inkorting nie.

Metode van toediening
Vir orale gebruik.
Tablette behoort heel ingesluk te word om die langdurig-vrystellende eienskappe te handhaaf. Die tablet moet nie vergruis of gekou word om sluk te vergemaklik nie. Tablette moet na 'n maaltyd geneem word.

4.3 Kontraïndikasies
Hipersensitiwiteit vir melatonien of enige van die hulpstowwe gelys in afdeling 6.1.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Outo-immuun siekte
Geen kliniese data bestaan rakende die gebruik van NOCTRIN 2 mg by individue met outo-immuun siektes nie. Daarom word NOCTRIN 2 mg nie aanbeveel vir gebruik by pasiënte met outo-immuun siektes nie.

Hulpstowwe
NOCTRIN 2 mg bevat laktosemonohidraat. Pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, die Lapp-laktase-tekort of glukose-galaktose-wanabsorpsie moet nie NOCTRIN 2 mg neem nie.

Pediatriese populasie
NOCTRIN 2 mg word nie aanbeveel vir gebruik by kinders en adolessente onder die ouderdom van 18 nie as gevolg van onvoldoende data oor die veiligheid en effektiwiteit.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Interaksiestudies is slegs by volwassenes uitgevoer.

Farmakokinetiese interaksies
- Daar is waargeneem dat melatonien CYP3A *in vitro* induseer teen supra-terapeutiese konsentrasies. Die kliniese relevansie van hierdie bevinding is onbekend. Indien induksie plaasvind, kan dit lei tot verminderde plasmakonsentrasies van medisyne wat gelyktydig toegedien word.
- Melatonien induseer nie CYP1A-ensieme *in vitro* teen supra-terapeutiese konsentrasies nie. Interaksies tussen melatonien en ander aktiewe stowwe as gevolg van die effek van melatonien se effek op CYP1A-ensieme sal waarskynlik nie beduidend wees nie.
- Melatonien se metabolisme word hoofsaaklik bemiddel deur CYP1A ensieme. Interaksies tussen melatonien en ander aktiewe stowwe as gevolg van die effek daarvan op CYP1A ensieme is dus moontlik.
- Omsigtigheid behoort uitgeoefen te word by pasiënte op fluvoksamien, wat melatonienvlakke verhoog (17-voudige hoër AOK en 'n 12-voudige hoër serum K_{maks}) deur die metabolisme daarvan deur hepatiese sitochroom P450 (CYP) isoënsieme CYP1A2 en CYP2C19 te inhibeer. Die kombinasie behoort vermy te word.
- Omsigtigheid behoort uitgeoefen te word by pasiënte op 5 - of 8 -metoksipsoraleen (5 -MOP en 8 -MOP), wat melatonienvlakke verhoog deur die metabolisme daarvan te inhibeer.
- Omsigtigheid behoort uitgeoefen te word by pasiënte op simetidien, 'n CYP2D-inhibeerder, wat melatonienvlakke verhoog deur die metabolisme daarvan te inhibeer.
- Die rook van sigarette mag melatonienvlakke verlaag as gevolg van die induksie van CYP1A2.
- Omsigtigheid behoort uitgeoefen te word by pasiënte op estrogene (bv. kontraseptiewe of hormoonvervangingsterapie), wat melatonienvlakke verhoog deur die metabolisme daarvan deur CYP1A1 en CYP1A2 te inhibeer.
- CYP1A2 inhibeerders soos kinolone kan lei tot verhoogde melatonien blootstelling.
- CYP1A2 induseerders soos karbamasepien en rifampisien kan lei tot verlaagde plasmakonsentrasies van melatonien.
- Daar is 'n groot hoeveelheid data in die literatuur beskikbaar rakende die effek van adrenergiese agoniste/antagoniste, opiaatagoniste/-antagoniste, antidepressante, prostaglandieninhibeerders, bensodiasepiene, triptofaan en alkohol, op endogene melatonienafskeiding. Of hierdie aktiewe stowwe met die dinamiese of kinetiese effekte van NOCTRIN 2 mg of andersom inmeng, al dan nie, is nie bestudeer nie.

Farmakodinamiese interaksies
- Alkohol behoort nie saam met NOCTRIN 2 mg geneem te word nie, omdat dit die effektiwiteit van NOCTRIN 2 mg ten opsigte van slaap, verminder.
- NOCTRIN 2 mg mag die sedatiewe eienskappe van bensodiasepiene en nie-bensodiasepien-hipnotika, soos saleplon, solpidem en sopikloon, versterk. In 'n kliniese proef was daar 'n duidelike bewys van 'n kortstondige farmakodinamiese interaksie tussen melatonien en solpidem een uur na gesamentlike dosering. Gelyktydige toediening het gelei tot verhoogde inkorting van aandag, geheue en koördinasie in vergelyking met solpidem alleen.
- NOCTRIN 2 mg is in studies saam met tioridasien en imipramien toegedien. Geen klinies beduidende farmakokinetiese interaksies is gevind nie. Die mede-toediening van melatonien het egter gelei tot verhoogde kalmerende gevoelens en probleme om take uit te voer in vergelyking met imipramien alleen, asook verhoogde gevoelens van deurmekaarheid in vergelyking met tioridasien alleen.

4.6 Vrugbaarheid, swangerskap en laktasie
Swangerskap
Veiligheid tydens swangerskap en laktasie is nie vasgestel nie. Daar is geen kliniese data beskikbaar oor gebruik tydens swangerskap nie. Weens die gebrek aan kliniese data, word gebruik by swanger vroue en by vroue wat van plan is om swanger te raak nie aanbeveel nie.

Borsvoeding
Endogene melatonien is in borsmelk gemeet, en dus word eksogene melatonien waarskynlik in menslike melk uitgeskei. Daarom word borsvoeding nie aanbeveel by vroue wat met melatonien behandel word nie.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik
Melatonien kan lomerigheid veroorsaak. Pasiënte moet vermy om gevaarlike aktiwiteite (soos bestuur of hantering van masjinerie) te onderneem na die neem van NOCTRIN 2 mg (sien afdeling 4.8).

4.8 Newe-effekte
Die volgende newe-effekte is in kliniese studies en spontane na-bemarkingsverslae aangemeld. Binne elke frekwensiegroepering word die ongewenste effekte aangebied in volgorde van afnemende erns.

a. Getabuleerde opsomming van newe-effekte

Sisteem-orgaanklas	Frekwensie	Ongewenste effek
Infeksies en infestasies	*Minder gereeld*	Herpes zoster
Bloed- en limfatiese sisteemversteurings	*Minder gereeld*	Leukopenie Trombositopenie
Immuunstelselversteurings	*Frekwensie onbekend*	Hipersensitiwiteitsreaksie
Metabolisme- en voedingsversteurings	*Minder gereeld*	Hipertrigliseriedemie Hipokalsemie Hiponatremie
Psigiatriese versteurings	*Minder gereeld*	Prikkelbaarheid Senuweeagtigheid Rusteloosheid Slaaploosheid Abnormale drome Nagmerries Angs Veranderde gemoedstemming Aggressie Agitasie Huil Spanningsimptome Disoriëntasie Vroeë oggend ontwakkerring Verhoogde libido Terneergedruktheid Depressie
Senusisteemversteurings	*Minder gereeld*	Migraine Hoofpyn Lusteloosheid Psigomotor hiperaktiwiteit Duiseligheid Lomerigheid Sinkopee Inkorting van geheue Aandag-versteurings Dromerige staat Rustelose bene Swak kwaliteit van slaap Parestesie
Oogversteurings	*Minder gereeld*	Verminderde gesigskerpte Dowwe visie Verhoogde lakrimasie
Oor- en doolhofversteurings	*Minder gereeld*	Posisionele vertigo Vertigo
Kardiale versteurings	*Minder gereeld*	Angina pectoris Palpitasies
Vaskulêre versteurings	*Minder gereeld*	Hipertensie Warm gloede
Gastroïntestinale versteurings	*Minder gereeld*	Abdominale pyn (boonste) Abdominale ongemak Gastritis Dispepsie Mondulserasie Naarheid Konstipasie Droë mond Gastroïntestinale ontsteltenis Gastro-esofageale refluks Blaasvorming van mondslymvies Tong ulserasie Braking Abnormale dermgeluide Winderigheid Speeksel hipersekresie Halitose
Hepato-bilière versteurings	*Minder gereeld*	Hiperbilirubinemie
Vel- en onderhuidse weefselversteurings	*Minder gereeld*	Dermatitis Nagtelike sweet Hiperhidrose Ekseem Eriteem Pruritiese uitslag Pruritus Droë vel Naelversteuring Hand dermatitis Psoriase
	Frekwensie onbekend	Angioedeem Edeem van die mond Tong edeem
Muskuloskeletale bindweefselversteurings	*Minder gereeld*	Pyn in die ledemate Artritis Spierkrampe Nek pyn Nagtelike krampe
Renale en urinêre versteurings	*Minder gereeld*	Glikosurie Proteinurie Poliurie Hematurie Nokturie
Voortplantingsisteem- en borsversteurings	*Minder gereeld*	Menopousale simptome Priapisme Prostatitis
	Frekwensie onbekend	Galaktorree
Algemene versteurings en t oedieningsarea toestande	*Minder gereeld*	Astenie Borspyn Moegheid Pyn Dorsheid
Ondersoeke	*Minder gereeld*	Gewigstoename Abnormale lewertoets Verhoogde hepatiese ensieme Abnormale bloed elektroliete Abnormale laboratorium toetse

b. 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. Gesondheidsorgverskaffers 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
Geen geval van oordosering is aangemeld nie. Indien oordosering plaasvind, behoort lomerigheid verwag te word. Die opruiming van die aktiewe stof word binne 12 uur na inname verwag. Geen spesiale behandeling is nodig nie.

5 FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
A 2.2 Sedatiewe, Hipnotika.
Farmakoterapeutiese Groep: Psigoleptika, melatonienreseptoragoniste.
ATK Kode: N05CH01.

Melatonien is 'n natuurlike hormoon wat die pineale klier geproduseer word en is struktureel verwant aan serotonien. Die aktiwiteit van melatonien by die melatonien 1 (MT1), melatonien 2 (MT2) en melatonien 3 (MT3) reseptore dra vermoedelik by tot die slaapbevorderende eienskappe, aangesien hierdie reseptore (hoofsaaklik MT1 en MT2) betrokke is by regulering van sirkadiese ritmes en slaapregulering.

5.2 Farmakokinetiese eienskappe
Absorpsie
Die absorpsie van oraal geneemde melatonien is volledig by volwassenes en mag met soveel as 50 % by bejaardes verminder wees. Die kinetika van melatonien is lineêr oor die reikwydte van 2 - 8 mg.

Biobeskikbaarheid is in die orde van 15 %. Daar is 'n beduidende eerstedeurgangseffek met 'n beraamde eerstedeurgangsmetabolisme van 85 %. T_{maks} word na 3 uur in 'n gevoerde staat bereik. Die tempo van melatonienabsorpsie en K_{maks} na orale toediening word deur voedsel beïnvloed. Die teenwoordigheid van voedsel het die absorpsie van die melatonien vertraag wat 'n latere (T_{maks} = 3,0 uur teenoor T_{maks} = 0,75 uur) en 'n laer piek plasmakonsentrasie in die gevoerde toestand (K_{maks} = 1 020 pg/mL teenoor K_{maks} = 1 176 pg/mL) veroorsaak het.

Verspreiding
Die *in vitro* plasmaproteïenbinding van melatonien is ongeveer 60 %. Melatonien is hoofsaaklik gebonde aan albumien, alfa1-suur glikoproteïen en hoëdigtheid lipoproteïen.

Biotransformasie
Eksperimentele data dui daarop dat isoënsieme CYP1A1, CYP1A2 en moontlik CYP2C19 van die sitochroom P450-stelsel by melatonienmetabolisme betrokke is. Die hoofmetaboliet, 6 -sulfatoksimelatonien (6 -S-MT), is onaktief. Die setel van biotransformasie is die lewer. Die uitskeiding van die metaboliet word binne 12 uur na inname voltooi.

Eliminasie
Die terminale halfleeftyd ($t_{½}$) is 3,5 - 4 uur. Eliminasie is deur renale uitskeiding van metaboliete, 89% as gesulfateerde- en glukuroniedkonjugate van 6 -hidroksimelatonien en 2 % word as onveranderde melatonien uitgeskei.

Geslag
'n 3- tot 4-voudige toename in K_{maks} is duidelik vir vroue in vergelyking met mans. 'n Vyf-voudige variasie in K_{maks} tussen verskillende lede van dieselfde geslag is ook waargeneem. Geen farmakodinamiese verskille tussen mans en vrouens is gevind nie, ondanks verskille in bloedvlakke.

Spesiale populasies
Bejaardes
Dit is bekend dat melatonienmetabolisme met ouderdom afneem. Oor 'n reikwydte van dosisse is hoër AOK- en K_{maks}-vlakke by ouer proefpersone in vergelyking met jonger proefpersone gerapporteer, wat 'n laer metabolisme van melatonien by bejaardes weerspieël. K_{maks}-vlakke van ongeveer 500 pg/mL by volwassenes (18 - 45) teenoor 1 200 pg/mL by bejaardes (55 - 69); AOK-vlakke van ongeveer 3 000 pg/h/mL by volwassenes teenoor 5 000 pg/h/mL by bejaardes.

Renale inkorting
Daar is geen akkumulasie na herhaalde dosering nie. Hierdie bevinding is vergelykbaar met die kort halfleeftyd by mense. Die vlakke wat vasgestel was in die bloed van pasiënte met eindstadium renale siekte op chroniese hemodialise, teen 23:00 (2 ure na toediening) na 1 en 3 weke se daaglikse toediening was 411,4 ± 56,5 en 432,0 ± 83,2 pg/mL onderskeidelik en is soortgelyk aan dié wat by gesonde vrywilligers gevind is na 'n enkele dosis van 2 mg melatonien.

Hepatiese inkorting
Die lewer is die primêre setel van melatonienmetabolisme en daarom lei hepatiese inkorting tot hoër endogene melatonienvlakke. Plasma-melatonienvlakke by pasiënte met sirrose is gedurende dagligure aansienlik verhoog. Pasiënte het 'n beduidende afname in die totale uitskeiding van 6 -sulfatoksimelatonien getoon in vergelyking met kontroles.

6 FARMSEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Laktosemonohidraat
Kalsiumwaterstof-fosfaat-dehidraat
Ammonio-metakriel-kopolimeer (Tipe B)
Gesuiwerde talk
Kolloïdale anhedriese silika
Magnesiumstearaat

6.2 Onverenigbaarheid
Onbekend.

6.3 Rakleeftyd
3 jaar.

6.4 Spesiale voorsorgmaatreëls tydens berging
Stoor teen of benede 25 ºC.
Beskerm teen lig.
Hou buite bereik van kinders.

6.5 Aard en inhoud van die houer
Tablette word verpak in PVC/PVDC/Al of Alu/Alu stulpverpakkings van 21, 30 of 7 tablette.
Die stulpverpakkings word dan in kartonbokse verpak.
Nie alle verpakkingsgroottes word moontlik bemark nie.

6.6 Spesiale voorsorgmaatreëls vir die wegdoen en ander hantering
Geen spesiale vereistes is nodig tydens wegdoening nie. Enige ongebruikte medisyne of afvalstowwe moet volgens plaaslike vereistes weggedoen word.

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8 REGISTRASIENOMMER(S)
NOCTRIN XR 2 MG: 52/2.2/0780

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
24 Mei 2022

10 DATE OF REVISION OF THE TEXT
N.A