APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS **S5**

1 NAME OF THE MEDICINE

YELATE 30, 30 mg, capsules

YELATE 60, 60 mg, capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

YELATE 30: Each delayed-release capsule contains enteric coated pellets of duloxetine hydrochloride equivalent to duloxetine 30 mg.

Contains sugar (sucrose).

YELATE 60: Each delayed-release capsule contains enteric coated pellets of duloxetine hydrochloride equivalent to duloxetine 60 mg.

Contains sugar (sucrose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

YELATE 30: White to off white spherical enteric coated pellets filled in size '3' hard gelatin capsules with opaque blue coloured cap and opaque white coloured body, imprinted 'RDY609' on cap and '30mg' on body with golden yellow ink.

YELATE 60: White to off white spherical enteric coated pellets filled in size '1' hard

gelatin capsules with opaque blue coloured cap and opaque green coloured body, imprinted 'RDY610' on cap and '60mg' on body with white ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

YELATE is indicated for the treatment of

- depression, as defined by DSM-1V Criteria

- diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration

Posology

Depression

YELATE should be initiated and maintained at a dose of 60 mg once daily without regard to meals.

Although doses of up to 120 mg per day have been used, the efficacy of 120 mg was not statistically significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Beneficial effects may be observed within one week of treatment but may take up to four weeks.

Diabetic peripheral neuropathic pain

YELATE should be administered at a dose of 60 mg once daily with or without food. Although doses of up to 120 mg per day have been used, the efficacy of 120 mg was not statistically significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Renal impairment

The initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function. (See "Pharmacokinetic properties", section 4.3 and section 4.4.)

Hepatic impairment

The initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function. (See "Pharmacokinetic properties", section 4.3 and section 4.4.)

Elderly patients

No dosage adjustment is recommended on the basis of age.

Children and adolescents

Safety and efficacy have not been established in patients under the age of 18 years.

Discontinuation of treatment

If the decision is made to discontinue treatment, YELATE dosage should be tapered gradually to minimise the risk of withdrawal reactions. (See section 4.4.)

Method of administration

Oral administration.

4.3 Contraindications

YELATE is contra-indicated in the following:

- Hypersensitivity to duloxetine or to any of the other ingredients of YELATE.
- Pregnancy and lactation.
- Severe impairment of hepatic function.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Concomitant use of monoamine oxidase inhibitors (MAOIs).

(See also section 4.4.)

- Uncontrolled narrow angle glaucoma or hypertension.

- Adolescents and children under the age of 18 years. (See section 4.4.)

4.4 Special warnings and precautions for use

MAOIs (Monoamine Oxidase Inhibitors):

YELATE should not be used within at least 14 days of discontinuing treatment with Monoamine Oxidase Inhibitors (MAOIs) and at least 5 days should be allowed after stopping YELATE, before starting a MAOI.

Children and adolescents

Safety and efficacy of YELATE have not been established in patients under the age of 18 years. (See section 4.3.)

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs.

Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy as contained in YELATE or early after treatment discontinuation.

Risk of suicide Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs.

A causal role for antidepressant medicine in inducing such behaviour has, however, not been established.

Patients being treated with YELATE should nevertheless be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants such as YELATE for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania. Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing YELATE, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
If the decision is made to discontinue treatment, YELATE should be tapered. (See section 4.2.)

Activation of mania/hypomania

YELATE should be used with caution in patients with a history of mania.

Seizures

YELATE should be used with caution in patients with a history of a seizure disorder.

Mydriasis

Caution is advised with YELATE in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma. Mydriasis has been reported to be associated with duloxetine.

Renal or hepatic impairment

A lower starting dose of YELATE should be used in these patients as increased plasma concentrations have been reported in patients with renal or hepatic impairment. (See "Pharmacokinetic properties", section 4.3 and section 4.2.)

Diabetes mellitus

Increases in fasting blood sugar and in total cholesterol have been reported in diabetic patients.

Increased blood pressure

YELATE is associated with an increase in blood pressure in some patients. Blood pressure monitoring is recommended in patients with known hypertension and/or other cardiac disease.

Elevated liver enzymes

Elevations in liver enzymes have been reported in some patients and severe elevation of liver enzymes (> 10 times the upper limit of normal) or liver injury with a cholestatic or mixed pattern have been reported less frequently.

YELATE should be used with caution in patients with substantial alcohol use or

pre-existing liver disease.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with YELATE treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs, tricyclic antidepressants or triptans), with medicines that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems.

If concomitant treatment with YELATE and other serotonergic medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Haemorrhage

There have been reports of bleeding abnormalities, such as ecchymoses, purpura, and gastrointestinal haemorrhage, with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine as in YELATE.

YELATE may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Caution is advised in patients taking anticoagulants and/or medicines known to affect platelet function, e.g., NSAIDs or acetylsalicylic acid (aspirin), and in patients with known bleeding tendencies.

Hyponatraemia

Hyponatraemia has been reported when administering YELATE, including cases with serum sodium lower than 110 mmol/l.

Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone

secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.

St John's Wort

Adverse reactions may be more common during concomitant use of YELATE and herbal preparations containing St John's Wort (*Hypericum perforatum*). (See section 4.5.)

Akathisia/Psychomotor Restlessness

The use of YELATE has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Carcinogenesis

Administration to female mice for two years caused an increase in hepatocellular adenomas and carcinomas at a high dose (144 mg/kg/day), but these were considered secondary to hepatic enzyme induction associated with centrilobular hypertrophy and vacuolation. The relevance of these preclinical observations in humans is unknown.

Takotsubo cardiomyopathy

Literature shows an association between increased levels of catecholamines and the risk of Takotsubo cardiomyopathy, suggesting that inhibition of androgen receptors by duloxetine results in increased catecholamines levels and

consequently cardiomyopathy.

Takotsubo cardiomyopathy is reversible upon discontinuation of YELATE and appropriate treatment.

Discontinuation of YELATE treatment

Symptoms reported after abrupt stopping of YELATE treatment include headache, nausea, vomiting, dizziness, insomnia, anxiety, fatigue, irritability, nightmares, diarrhoea, hyperhidrosis, vertigo and paraesthesia.

It is therefore recommended, if YELATE is to be discontinued after more than one week of therapy the dose be tapered and that the withdrawal be gradual over at least a period of two weeks. The patient should be monitored to minimise the risk of withdrawal reaction. (See section 4.2.)

Sucrose

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take YELATE.

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interaction with other medicines and other forms of interaction:

Monoamine Oxidase Inhibitors (MAOIs)

Due to the risk of serotonin syndrome, YELATE should not be given in combination with MAOIs. See sections 4.3, 4.4.

Medicines metabolised by CYP1A2

The pharmacokinetics of theophylline, a CYP1A2 substrate, was reported not to be

significantly affected by co-administration of a duloxetine dose of 60 mg twice a day.

This suggests that YELATE is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Inhibitors of CYP1A2

Concomitant use of YELATE with inhibitors of CYP1A2 will result in higher concentrations of duloxetine because CYP1A2 is involved in the metabolism of duloxetine.

Fluvoxamine (100 mg once daily), an inhibitor of CYP1A2, decreases the apparent plasma clearance of duloxetine by about 77 %.

Caution is therefore necessary when YELATE is administered with inhibitors of CYP1A2 (e.g. quinolone antibiotics) and a lower dose of YELATE is advised.

Medicines metabolised by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6.

YELATE (60 mg twice daily), administered with a single dose of desipramine, a CYP2D6 substrate, increases the AUC of desipramine 3-fold.

At a 40 mg twice daily dose, duloxetine increased the steady state AUC of tolterodine (2 mg twice daily) by 71 %, although the pharmacokinetics of its 5-hydroxyl metabolite was not affected.

Caution is therefore advised when YELATE is co-administered with medicines with narrow therapeutic indices, if they are metabolised predominantly by CYP2D6.

Inhibitors of CYP2D6

Concomitant use of YELATE with inhibitors of CYP2D6 may result in higher concentrations of duloxetine because CYP2D6 is involved in the metabolism of duloxetine.

Paroxetine (20 mg twice daily) decreases the apparent plasma clearance of duloxetine by about 37 %.

Taking YELATE with inhibitors of CYP2D6 (e.g. SSRIs) should therefore be done with caution.

Medicines acting on the central nervous system (CNS)

Caution is advised when YELATE is taken in combination with other centrally acting medicines and substances, including alcohol and sedative medicines (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Concomitant use of other medicines with serotonergic activity (e.g. SNRIs, SSRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs, St John's Wort (*Hypericum perforatum*), triptans, tramadol, pethidine and tryptophan) may result in serotonin syndrome.

Medicines highly bound to plasma protein

Duloxetine is highly bound to plasma proteins (> 90 %). Therefore, administration of YELATE to a patient taking another medicine that is highly protein bound may cause an increase in free concentrations of either medicine.

Anticoagulants and antiplatelet medicines

As YELATE may increase the risk of bleeding, caution is advised when YELATE is given with warfarin or medicines known to affect platelet function.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of YELATE in pregnancy has not been established. (See section 4.3.)

Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth (see sections 4.4, 4.8).

Breastfeeding

Safety of YELATE in mothers breastfeeding their infants has not been established. YELATE is excreted into the milk of lactating women. (See section 4.3.)

Impairment of fertility

Reproductive performance was reported not to have been affected in male rats receiving duloxetine as contained in YELATE (45 mg/kg/day).

In female rats receiving 45 mg/kg/day, reproductive toxicity was demonstrated by a decrease in maternal food consumption and body mass, oestrus cycle disruption, depressions in live birth indices and progeny survival and progeny growth retardation. The no-observed-effect-level (NOEL) for maternal toxicity, reproductive toxicity and developmental toxicity in the female fertility study was 10 mg/kg/day. The relevance of these preclinical observations in humans is unknown.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking YELATE as it may be associated with undesirable effects such as sedation and dizziness.

4.8 Undesirable effects

Infections and infestations

Less frequent: Laryngitis

Immune system disorders

Less frequent: Anaphylactic reaction, hyper-sensitivity disorder

Endocrine disorders

Less frequent: Hypothyroidism

Metabolism and nutrition disorders

Frequent: Decreased appetite

Less frequent: Dehydration, hyponatraemia, hyperglycaemia (reported especially in diabetic patients), SIADH

Psychiatric disorders

Frequent: Insomnia, anxiety, feeling jittery, nervousness, restlessness, tension, sleep disorder, agitation, abnormal dreams

Less frequent: Bruxism, disorientation, mania, apathy, suicidal ideation, suicidal behaviour, hallucinations, aggression and anger

Nervous system disorders

Frequent: Dizziness, headache, lethargy, somnolence, hypersomnia, sedation, tremor, dysgeusia, paraesthesia

Less frequent: Convulsions, serotonin syndrome, disturbance in attention, dyskinesia, poor quality sleep, myoclonus, restless legs syndrome, psychomotor restlessness, extra-pyramidal symptoms

Eye disorders

Frequent: Blurred vision

Less frequent: Mydriasis, visual disturbance, glaucoma

Ear and labyrinth disorders

Frequent: Vertigo

Less frequent: Ear pain, tinnitus

Cardiac disorders

Frequent: Palpitations

Less frequent: Tachycardia, supra-ventricular arrhythmia, mainly atrial fibrillation,

Takotsubo cardiomyopathy

Vascular disorders

Frequent: Flushing, hot flushes

Less frequent: Peripheral coldness, orthostatic hypotension, syncope, hypertension, hypertensive crisis

Respiratory, thoracic and mediastinal disorders

Frequent: Yawning

Less frequent: Throat tightness, epistaxis

Gastrointestinal disorders

Frequent: Constipation, dry mouth, nausea, vomiting, diarrhoea, dyspepsia (includes stomach discomfort), flatulence, abdominal pain, gastrointestinal haemorrhage

Less frequent: Eructation, gastroenteritis, stomatitis, breath odour, gastritis, dysphagia, haematochezia

Hepato-biliary disorders

Less frequent: Hepatitis, hepatic failure with or without jaundice (sometimes fatal), acute liver injury

Skin and subcutaneous tissue disorders

Frequent: Hyperhidrosis

Less frequent: Night sweats, photosensitivity reaction, rash, angioedema, Stevens-Johnson syndrome, urticaria, pruritus, ecchymosis, cold sweat, dermatitis contact

Musculoskeletal, connective tissue and bone disorders

Frequent: Musculoskeletal pain (includes myalgia and neck pain), muscle spasm

Less frequent: Muscle tightness, muscle twitching, akathisia, trismus

Renal and urinary disorders

Frequent: Pollakiuria

Less frequent: Nocturia, urinary hesitation, urinary retention, dysuria, polyuria, urine flow decreased, urine odour abnormal

Reproductive system and breast disorders

Frequent:

Decreased libido

Females: Anorgasmia, abnormal orgasm

Less frequent:

Sexual dysfunction, galactorrhoea, hyperprolactinaemia

Males: Ejaculation disorder, delayed ejaculation, erectile dysfunction, testicular pain

Females: Menopausal symptoms, gynaecological haemorrhage, menstrual disorder, postpartum haemorrhage

General disorders and administration site conditions

Frequent: Fatigue, asthenia, rigors, falls

Less frequent: Feeling abnormal, chills, feeling hot, feeling cold, malaise, increased thirst, gait disturbance, chest pain

Investigations

Frequent: Decreased weight, increased blood pressure

Less frequent: Increased weight, hepatic laboratory related findings (includes increased AST, increased ALT, increased gamma-glutamyl transferase, increased alkaline phosphatase, increased bilirubin), blood cholesterol increased, blood creatine phosphokinase increased, blood potassium increased

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 provders 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

Signs and symptoms

In post marketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as approximately 1000 mg. Signs and symptoms of overdose (most with mixed medicines) include serotonin syndrome, somnolence, vomiting, coma, tachycardia and seizures.

The predicted signs would be related to the central nervous and gastrointestinal systems (e.g. tremors, clonic convulsions, ataxia, emesis and decreased appetite).

Management of overdose

No specific antidote is known, but if serotonin syndrome ensues, specific treatment, (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine as in YELATE has a large volume of distribution and forced diuresis, haemoperfusion and exchange perfusion are unlikely to be beneficial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 1.2 Psychoanaleptics (antidepressants)

Duloxetine is a serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor (SNRI) and is chemically unrelated to tricyclic and tetracyclic antidepressant medicines.

Duloxetine weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors.

Duloxetine dose-dependently increased extracellular levels of serotonin and norepinephrine in various brain areas of animals.

Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and norepinephrine neurotransmission in the central nervous system (CNS).

The mechanism of pain alleviation is unknown.

The mechanism of action of duloxetine in the treatment of depression is presumed to be due to its inhibition of neuronal uptake of serotonin and norepinephrine and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS.

5.2 Pharmacokinetic properties

Absorption: Duloxetine is well absorbed after oral administration, with the C_{max} occurring 6 hours post-dose. Food delays the time to reach peak concentration

from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). Steady-state plasma concentration is achieved after 3 days of dosing.

Distribution: Duloxetine is highly bound (> 90 %) to plasma proteins, primarily to albumin and alpha-1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Metabolism: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine, sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine). Circulating metabolites are not pharmacologically active.

Excretion: The mean elimination half-life of duloxetine is 12,1 hours. The mean plasma clearance of duloxetine is 101 l/hr.

Special populations

Gender: Pharmacokinetic differences have been identified between males and females. The mean plasma clearance is 9 % to 55 % lower in females, but the duloxetine half-life is similar in males and females.

Smoking status: Duloxetine bioavailability appears to be 34 % lower in smokers than in non-smokers.

Age: Pharmacokinetic differences have been identified between middle aged and elderly females (AUC is 24 % higher and half-life is 4,3 hours longer in the elderly).

Renal impairment: End-stage renal disease patients receiving chronic intermittent haemodialysis had 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Therefore, a lower dose should be used in patients with clinically significant renal impairment. (See section 4.3.)

Hepatic impairment: The half-life of duloxetine is 34 hours longer in patients with cirrhosis of the liver and clearance is approximately 15 % of that for age and gender-matched healthy subjects.

Therefore, a lower dose should be used for patients with mild to moderate liver impairment. (See sections 4.2 and 4.3.)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

YELATE 30

Capsule content

Glycine

Hydroxypropyl methylcellulose

Hypromellose phthalate

Talc

Triethyl citrate.

Capsule shell ingredients

FD&C blue 2

Gelatin

Sodium lauryl sulphate

Titanium dioxide

Printing ink (golden yellow)

Shellac

Propylene glycol

Yellow iron oxide (E172).

YELATE 60

Capsule content

Glycine

Hydroxypropyl methylcellulose

Hypromellose phthalate

Talc

Triethyl citrate.

Capsule shell ingredients

FD&C blue 2

Gelatin

Sodium lauryl sulphate

Titanium dioxide.

Printing ink (white)

Shellac

Potassium hydroxide

Propylene glycol

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

The blisters must be kept in the carton until required for use.

The HDPE containers must be kept tightly closed.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

HDPE containers: The capsules are packaged in white HDPE containers with white plastic caps containing 30/60/90/100/500/1000 capsules.

Blister packs: The capsules are packed in Alu/Alu blisters of 7/10 capsules per blister strip.

Blisters strips (4 x 7 or 3 x 10 resulting in a pack of 28 or 30 capsules) are packed in plain white duplex cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd

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Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

YELATE 30: 44/1.2/0114

YELATE 60: 44/1.2/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 December 2012

10 DATE OF REVISION OF TEXT

30 September 2023