1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

CYMGEN 30 mg capsules

CYMGEN 60 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CYMGEN 30

Each delayed-release capsule of CYMGEN 30 for oral administration contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg of duloxetine that are designed to prevent degradation of the medicine in the acidic environment of the stomach.

Contains sugar: Sucrose 55,5 mg

For full list of excipients, see section 6.1.

CYMGEN 60

Each delayed-release capsule of CYMGEN 60 for oral administration contains enteric-coated pellets of duloxetine hydrochloride equivalent to 60 mg of duloxetine that are designed to prevent degradation of the medicine in the acidic environment of the stomach.

Contains sugar: Sucrose 110,6 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Delayed release capsules

CYMGEN 30,

Hard gelatin capsule size ‘3’ opaque blue cap and opaque white body, imprinted with ‘F38’ on cap and body in green ink that contains white to light greyish white pellets.

CYMGEN 60,

Hard gelatin capsule size ‘1’ opaque blue cap and opaque green body, imprinted with ‘F39’ on cap and body in white ink that contains white to light greyish white pellets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CYMGEN is indicated for:

- the treatment of depression (as defined by DSM-IV criteria).
- the treatment of diabetic peripheral neuropathic pain (DPNP).

4.2. Posology and method of administration

Posology

Depression

CYMGEN should be initiated and maintained at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used, the efficacy of the 120 mg dose was not statistically different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Therapeutic response is usually seen after 2 to 4 weeks of treatment.

Diabetic peripheral neuropathic pain

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

Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely.

The therapeutic benefit should be reassessed regularly (at least every three months).

Special populations

Renal impairment

Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function (see sections 4.3, 4.4, and 5.2).

Hepatic impairment

Initial dose should be 30 mg once daily in patients with mild to moderate impairment of hepatic function (see sections 4.3, 4.4, and 5.2).

Elderly

No dosage adjustment is recommended for elderly patients on the basis of age. However, caution should be exercised when treating the elderly, especially with 120 mg of CYMGEN per day for depression, for which data are limited (see sections 4.4 and 5.2).

Paediatric population

CYMGEN is not indicated for use in patients under 18 years of age (see section 4.3).

Discontinuation of treatment

Abrupt discontinuation should be avoided. Symptoms associated with discontinuation of CYMGEN, and other selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. When stopping treatment with CYMGEN the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8).

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered.

Subsequently, the medical practitioners may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

4.3. Contraindications

CYMGEN is contraindicated in:

- Patients with hypersensitivity to duloxetine or to any excipients in CYMGEN (see section 6.1).
- Severe impairment of hepatic function (Child-Pugh C).
- Advanced renal impairment (creatinine clearance < 30 ml/min).
- Concomitant use of monoamine oxidase inhibitors (MAOIs) including linezolid (see section 4.4 and 4.5).
- Patients under 18 years of age (see sections 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

MAOIs (Monoamine Oxidase Inhibitors):

CYMGEN should not be used within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of CYMGEN, at least 5 days should be allowed after stopping CYMGEN, before starting a MAOI.

Suicide and major depressive disorder

Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision of patients, and in particular those at high-risk should accompany medicine

therapy, especially in early treatment and following dose changes. Cases of suicidal ideation and suicidal behaviours have been reported during CYMGEN therapy or after early treatment discontinuation (see section 4.8).

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicidal behaviour and should receive careful monitoring during treatment. Reports of antidepressant medicines in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

In major depressive disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm.

Physicians should encourage patients to report any distressing thoughts or feelings at any time. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Activation of mania/hypomania

CYMGEN should be used cautiously in patients with a history of mania or a diagnosis of bipolar disorder.

Seizures

CYMGEN should be used cautiously in patients with a history of a seizure disorder.

Mydriasis

Mydriasis has been reported in association with duloxetine, as in CYMGEN; therefore, caution

should be used when prescribing CYMGEN in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Renal or hepatic impairment

Increased plasma concentrations of CYMGEN occur in patients with renal impairment or hepatic impairment. A lower starting dose should be used in such patients.

An initial dose of 30 mg once daily should be used in patients with renal impairment and those with mild to moderate hepatic impairment (Child-Pugh A and B) (see sections 4.2, 4.3 and 5.2).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with CYMGEN treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs tricyclic antidepressants or triptans with buprenorphine-containing medicines), with medicines that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If concomitant treatment with CYMGEN 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.

St John's Wort

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

Increased blood pressure and heart rate

CYMGEN is associated with an increase in blood pressure, and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine, as in CYMGEN. Cases of hypertensive crisis have been reported with duloxetine, as in CYMGEN, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate, especially during the first month of treatment.

CYMGEN should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine, as in CYMGEN, is used with medicines that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine, as in CYMGEN, either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension, CYMGEN should not be initiated.

Hepatitis/elevated liver enzymes

Severe elevations of liver enzymes (> 10 times the upper limit of normal) or liver injury with a cholestatic or mixed pattern, hepatitis, and jaundice have been reported with duloxetine, as in CYMGEN (see section 4.8). These were usually transient and self-limiting, or resolved upon discontinuation of CYMGEN. Most of these occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. It is in some cases associated with excessive alcohol use or pre-existing liver disease, CYMGEN should be used in caution in patients

with substantial alcohol use, in patients with pre-existing liver disease or in patients treated with other medicines associated with hepatic injury.

Sexual dysfunction

SSRIs/SNRIs such as duloxetine, as in CYMGEN, may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI such as duloxetine, as in CYMGEN.

Carcinogenesis, mutagenesis and impairment of fertility:

Carcinogenesis

Duloxetine, as in CYMGEN, was administered in the diet to rats and mice for 2 years. In rats, duloxetine, as in CYMGEN, did not cause any increase in incidence of expected or unusual neoplasms or decrease in the latency for any tumour type. In female mice receiving duloxetine, as in CYMGEN, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation. The relevance of this data in humans is unknown.

Mutagenesis

Duloxetine, as in CYMGEN, has demonstrated no mutagenic potential in a battery of *in vitro* and *in vivo* genotoxicity tests.

Impairment of fertility

Reproductive performance was not affected in male rats receiving duloxetine, as in CYMGEN

(45 mg/kg/day). In female rats receiving duloxetine, as in CYMGEN (45 mg/kg/day), reproductive toxicity was demonstrated by a decrease in maternal food consumption and body weight, oestrous cycle disruption, depression 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 this preclinical data in humans is unknown (see section 4.6).

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 CYMGEN and appropriate treatment.

Haemorrhage

CYMGEN, may increase the risk of bleeding events, such as ecchymoses, purpura, and gastrointestinal bleeding (see section 4.8). CYMGEN may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). Therefore, caution is advised in patients taking CYMGEN concomitantly with anticoagulants and/or medicines known to affect platelet function (e.g. NSAIDs or aspirin), and in patients with known bleeding tendencies (see section 4.5).

Hyponatraemia

Hyponatraemia has been reported when administering duloxetine, as in CYMGEN, including cases with serum sodium lower than 110 mmol/L. Hyponatraemia may be due to a syndrome of

inappropriate anti-diuretic hormone secretion (SIADH) (see section 4.8). 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.

Hyponatraemia may present with nonspecific signs and symptoms (such as dizziness, weakness, nausea, vomiting, confusion, somnolence, and lethargy). Signs and symptoms associated with more severe cases have included syncopal episodes, falls and seizure.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see sections 4.2 and 4.8). Adverse events seen on abrupt treatment discontinuation have been reported. They occurred in approximately 45 % of patients treated with duloxetine, as in CYMGEN, and 23 % of patients taking placebo.

The risk of withdrawal symptoms seen with SSRIs and SNRIs such as duloxetine, as in CYMGEN, may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 3 months or more). It is therefore advised that CYMGEN should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Akathisia/Psychomotor restlessness

The use of CYMGEN 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 (see section 4.8). 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.

Elderly

Data on the use of CYMGEN 120 mg in elderly patients with depression are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.1).

Paediatric population

CYMGEN is contraindicated for use in patients under 18 years of age (see sections 4.3 and 4.8). Duloxetine, should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, and anger) were more frequently observed among children, adolescents, and young adults (< 25 years of age) treated with antidepressants such as duloxetine, compared to those treated with placebo. In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

Excipients

CYMGEN contains sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

MAOIs (Monoamine Oxidase Inhibitors): Due to the risk of serotonin syndrome, CYMGEN should not be used in combination with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) including linezolid and moclobemide or within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of CYMGEN, at least 5 days should be allowed after stopping CYMGEN, before starting a MAOI (see sections 4.3 and 4.4).

Medicines metabolised by CYP1A2: In a clinical study, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine, as in CYMGEN, (60 mg twice daily). These results suggest that duloxetine, as in CYMGEN, is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine, as in CYMGEN, metabolism, concomitant use of duloxetine, as in CYMGEN, with inhibitors of CYP1A2 will result in higher concentrations of duloxetine, as in CYMGEN. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine, as in CYMGEN, by about 77 % and increased AUC_{o-t} 6-fold. Therefore, duloxetine, as in CYMGEN, should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine. Caution is advised if administering duloxetine, as in CYMGEN, with inhibitors of CYP1A2 (e.g. quinolone antibiotics) and a lower duloxetine, as in CYMGEN, dose should be used.

Medicines metabolised by CYP2D6: duloxetine, as in CYMGEN, is a moderate inhibitor of CYP2D6. When duloxetine, as in CYMGEN, was administered at the dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine, as in CYMGEN (40 mg twice daily) increased the steady-state AUC of tolterodine (2 mg twice daily) by 71 % but did not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Therefore, caution should be used if duloxetine, as in CYMGEN, is co-administered with medicines that are predominately metabolised by the CYP2D6 (risperidone, tricyclic antidepressants (TCAs), such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Inhibitors of CYP2D6: Because CYP2D6 is involved in CYMGEN metabolism, concomitant use of CYMGEN with inhibitors of CYP2D6 may result in higher concentrations of CYMGEN. Paroxetine (20 mg once daily) decreased the apparent plasma clearance of CYMGEN by about 37 %. Caution is advised if administering CYMGEN with inhibitors of CYP2D6 (e.g. SSRIs).

CNS medicines: The risk of using duloxetine, as in CYMGEN, in combination with other CNS-active medicines has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when duloxetine, as in CYMGEN, is taken in combination with other centrally acting medicines and substances, including alcohol and sedative medicines (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbitone, sedative antihistamines).

Serotonergic medicines: Serotonin syndrome has been reported in patients using SSRIs/SNRIs

such as duloxetine, as in CYMGEN, concomitantly with serotonergic medicines. Caution is advised if duloxetine, as in CYMGEN, is used concomitantly with serotonergic medicines like SSRIs, SNRIs, tricyclics antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort (*Hypericum perforatum*) or triptans, tramadol, pethidine, and tryptophan (see sections 4.3 and 4.4).

Buprenorphine-containing medicines: CYMGEN should be used cautiously when co-administered with buprenorphine-containing medicines as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Oral contraceptives and other steroidal medicines: Results of *in vitro* studies demonstrate that duloxetine, as in CYMGEN, does not induce the catalytic activity of CYP3A. Specific *in vivo* medicine interaction studies have not been performed.

Anticoagulants and antiplatelet medicines: Caution should be exercised when CYMGEN is combined with oral anticoagulants or antiplatelet medicines due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction (see section 4.4). Furthermore, increases in INR values have been reported when duloxetine, as in CYMGEN, was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine, as in CYMGEN, with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Antacids and H_2 antagonists: Co-administration of duloxetine, as in CYMGEN, with aluminium- and magnesium-containing antacids, or duloxetine, as in CYMGEN, with famotidine, had no

significant effect on the rate or extent of duloxetine, as in CYMGEN, absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50 % lower plasma concentrations of duloxetine, as in CYMGEN, compared with non-smokers.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety in pregnant women has not been established.

CYMGEN should not be used during pregnancy. Discontinuation symptoms (e.g. hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures) may occur in the neonate after maternal CYMGEN use near term (see section 4.3). The majority of cases have occurred either at birth or within a few days of birth.

Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine, as in CYMGEN, lower than the maximum clinical exposure.

Two large observational studies do not suggest an overall increased risk of major congenital malformation (one from the US including 2,500 exposed to duloxetine, as in CYMGEN, during the first trimester and one from the EU including 1,500 exposed to duloxetine, as in CYMGEN, during the first trimester). The analysis on specific malformations such as cardiac malformations show

inconclusive results.

In the EU study, maternal exposure to duloxetine, as in CYMGEN, during late pregnancy (at any time from 20 weeks gestational age to delivery) was associated with an increased risk for pre-term birth (less than 2-fold, corresponding to approximately 6 additional premature births per 100 women treated with duloxetine, as in CYMGEN, late in pregnancy). The majority occurred between 35 and 36 weeks of gestation.

Observational data indicated an increased risk (less than 2-fold) of postpartum haemorrhage following duloxetine, as in CYMGEN, exposure within the month prior to birth (see sections 4.4 and 4.8).

Epidemiological data have suggested that the use of SSRIs, such as duloxetine, as in CYMGEN, in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with CYMGEN, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

Breastfeeding

The safety of CYMGEN has not been established in breastfeeding women. CYMGEN is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0,14 % of the maternal dose. Because the safety of CYMGEN in infants is not known, the use of CYMGEN while breastfeeding is not recommended (see section 4.3).

Fertility

In animal studies, duloxetine, as in CYMGEN, had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

4.7. Effects on ability to drive and use machines

CYMGEN has minor influence on the ability to drive or operate machinery.

Since adverse reactions such as sedation and dizziness have been reported in patients receiving CYMGEN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CYMGEN does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) *Summary of the safety profile*

The most commonly reported adverse reactions in patients treated with duloxetine, as in CYMGEN, were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate; they usually started early in therapy, and most tended to subside even as therapy was continued.

b) Tabulated list of adverse reactions

The table below gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials for duloxetine as contained in CYMGEN

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Laryngitis.	
Immune system disorders		Anaphylactic reaction, hyper-sensitivity disorder	
Endocrine disorders		Hypothyroidism.	

Metabolism and nutrition disorders	Decreased appetite[11] (includes anorexia. Previously listed under anorexia and decreased appetite, or anorexia and appetite decreased).	Dehydration, hyperglycaemia (reported especially in diabetic patients), hyponatraemia, Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH),[6]	
Psychiatric disorders	Insomnia (also includes middle insomnia, early morning awakening, and initial insomnia), abnormal orgasm (also includes anorgasmia), libido decreased (also includes loss of libido), anxiety, sleep disorder, agitation (also includes feeling jittery, nervousness, restlessness, tension and psychomotor agitation)[6] abnormal dreams (includes nightmares), MDD only,	Bruxism, disorientation (includes confusional state) apathy, suicidal ideation,[5,7] suicidal behaviour,[5,7] hallucinations, mania, aggression and anger.[4]	
Nervous system disorders	Headache (placebo rate was more than duloxetine rate), dizziness, lethargy, somnolence[11] (also includes hypersomnia, sedation) tremor, dysgeusia, paraesthesia (includes hypoaesthesia, hypoaesthesia facial, and paraesthesia oral).	Disturbance in attention, dyskinesia, poor quality sleep, myoclonus, akathisia,[6] restless leg syndrome, convulsions[1,6,11] (seizures,[11]), extrapyramidal symptoms,[6] serotonin syndrome,[6,11]	
Eye disorders	Vision blurred.	Mydriasis, Visual impairment, glaucoma.	
Ear and labyrinth disorders	Tinnitus.[1]	Vertigo, ear pain.	
Cardiac disorders	Palpitations.	Tachycardia,[11] supra-ventricular dysrhythmia, mainly atrial fibrillation, Takotsubo cardiomyopathy.	
Vascular disorders	Blood pressure increase (includes blood pressure systolic diastolic increased, systolic hypertension, diastolic hypertension, essential hypertension),[3] flushing	Peripheral coldness, orthostatic hypotension,[2] hypertension,[3,7] hypertensive crisis.[3,6] Syncope.[2]	

Respiratory, thoracic and mediastinal disorders	Yawning.	Throat tightness, epistaxis. interstitial lung disease,[10] eosinophilic pneumonia.[6]	
Gastrointestinal disorders	Constipation, dry mouth, nausea, diarrhoea, vomiting,[11] abdominal pain, dyspepsia (includes stomach discomfort), flatulence.	Eructation, gastroenteritis, stomatitis, breath odour, gastritis, gastrointestinal haemorrhage,[7] dysphagia, haematochezia, microscopic colitis.[9]	
Hepatobiliary disorders		Hepatitis,[3] acute liver injury, hepatic failure,[6] jaundice.[6]	
Skin and subcutaneous tissue disorders	Hyperhidrosis, rash.	Night sweats, photosensitivity reaction, cold sweat, dermatitis contact, urticaria, increased tendency to bruise, Stevens-Johnson Syndrome (SJS),[6] angio-neurotic oedema,[6] cutaneous vasculitis,	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain (includes myalgia and neck pain), muscle spasm.	Muscle tightness (includes musculoskeletal stiffness), muscle twitching, trismus.	
Renal and urinary disorders	Pollakiuria, dysuria.	Nocturia, urinary hesitation, urinary retention, polyuria, urine flow decreased, urine odour abnormal.	
Reproductive system and breast disorders	Erectile dysfunction, ejaculation disorder (also includes ejaculation failure and ejaculation dysfunction), ejaculation delayed.	menopausal symptoms, sexual dysfunction, gynaecological haemorrhage, menstrual disorder, testicular pain, galactorrhoea, hyper-prolactinaemia, postpartum haemorrhage.[6]	
General disorders and administrative site conditions	Fatigue (also includes asthenia), abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort and gastrointestinal pain), falls.[8]	Feeling abnormal, feeling cold, feeling hot, malaise, thirst, gait disturbance, chest pain.[7] chills.	

Investigations	Weight decreased	Hepatic lab related findings (includes alanine aminotransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyl transferase increased, blood alkaline phosphatase increased, blood bilirubin increased), weight increased, blood cholesterol increased, blood creatine phosphokinase increased, blood potassium increased.	

[1]Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.

[2]Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

[3]See section 4.4

[4]Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

[5]Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine, as in CYMGEN, therapy or early after treatment discontinuation (see section 4.4).

[6]Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

[7]Not statistically significantly different from placebo.

[8]Falls were more common in the elderly (≥ 65 years old)

[9]Estimated frequency based on all clinical trial data

[10]Estimated frequency based on placebo-controlled clinical trials.

[11]Signs and symptoms of overdose with CYMGEN alone or with mixed medicines.

c) Description of selected adverse reactions

Discontinuation symptoms: Discontinuation of duloxetine, as in CYMGEN, (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams, nightmares), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported withdrawal symptoms.

Generally, for SSRIs and SNRIs such as duloxetine, as in CYMGEN, events are mild to moderate and self-limiting; however, in some patients these may be severe and/or prolonged. It is therefore advised that when duloxetine, as in CYMGEN, treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Clinical trials:

Duloxetine, as in CYMGEN, treatment in placebo-controlled clinical trials was associated with mean increases from baseline to endpoint in ALT, AST, CPK and potassium. In some cases, abnormal values were observed for these analytes in duloxetine, as in CYMGEN, treated patients. The heart rate-corrected QT interval in duloxetine, as in CYMGEN-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine, as in CYMGEN-treated and placebo-treated patients.

Glucose regulation:

In three clinical trials of CYMGEN for the treatment of diabetic peripheral neuropathic pain, small

but statistically significant increases in fasting blood glucose were observed in duloxetine, as in CYMGEN-treated patients. HbA_{1c} was stable in both duloxetine, as in CYMGEN-treated and placebo-treated patients. The mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 9,048 mmol/L (176 mg/dl), and the mean baseline haemoglobin A_{1c} (HbA_{1c}) was 7,81 %. In the 12-week acute treatment phase of these studies, small increases in fasting blood glucose were observed in duloxetine, as in CYMGEN-treated patients. HbA_{1c} was stable in both the duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine, as in CYMGEN, and the routine care groups, but the mean increase was 0,3 % greater in the duloxetine, as in CYMGEN-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine, as in CYMGEN-treated patients while those laboratory tests showed a slight increase in the routine care group.

d) Paediatric population

CYMGEN is contraindicated in patients under 18 years of age (see section 4.3).

In children there have been reports of hostility, suicidal ideation and self-harm (see section 4.4).

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 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

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

Cases of acute ingestions with duloxetine, as in CYMGEN up to 5 400 mg, alone or in combination with other medicines, were reported, none being fatal.

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 1 000 mg. Signs and symptoms of overdose (CYMGEN alone or with mixed medicines) included serotonin syndrome, somnolence, vomiting, coma, tachycardia and seizures. The predicted signs would be related to the central nervous and gastrointestinal systems (e.g. tremors, chronic convulsions, ataxia, emesis and decreased appetite).

Treatment

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. Activated charcoal may be useful in limiting absorption. CYMGEN 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

Category and Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX21

Mechanism of action

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

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 pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the CNS.

The presumed mechanism of action of duloxetine in the treatment of depression is thought 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.

Elderly

The effect of duloxetine 60 mg once a day in elderly depressed patients (≥ 65 years) was

specifically examined in a study that showed a statistically significant difference in the reduction of the HAMD-17 score for duloxetine-treated patients compared to placebo. Tolerability of duloxetine 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120 mg per day) are limited and thus, caution is recommended when treating this population.

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 concentrations are achieved after 3 days of dosing.

Distribution

Duloxetine is highly bound (> 90 %) to plasma proteins; primarily to albumin and α1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation

Duloxetine is extensively metabolised. 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.

Elimination

The mean elimination half-life of duloxetine is 12,1 hours. The mean plasma clearance of duloxetine is 101 L/hr. The metabolites are excreted principally in urine.

Special populations:

Gender: Pharmacokinetic differences have been identified between males and females. The mean plasma clearance was 9 % to 55 % lower in females, but the duloxetine half-life was similar between males and females. Some women may need a lower dose.

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

Age: Pharmacokinetic differences have been identified between middle age 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 patients. Therefore, a lower dose should be used in patients with clinically significant renal impairment (see sections 4.2 and 4.3).

Hepatic impairment: The half-life of duloxetine was 34 hours longer in patients with moderate cirrhosis of the liver, Child Pugh B, and exposure as AUC was approximately increased four-fold. Clearance was approximately 15 % of that for age and gender-matched healthy patients. Therefore, a lower dose should be used for patients with mild to moderate liver impairment. However, duloxetine is contraindicated in severe impairment of hepatic function (Child-Pugh C) (see sections 4.2 and 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

CYMGEN 30 mg:

Carmoisine (E122), FD&C blue no. 2 aluminium lake (E132), gelatin, hypromellose, hypromellose acetate succinate, iron oxide yellow (E172), patent blue V (E131), propylene glycol, shellac

(E904), sodium lauryl sulfate, sucrose, sugar spheres, talc, triethyl citrate, titanium dioxide (E171).

CYMGEN 60 mg

Carmoisine (E122), gelatin, hypromellose, hypromellose acetate succinate, iron oxide yellow (E172), patent blue V (E131), povidone, propylene glycol, shellac (E904), sodium lauryl sulfate, sucrose, sugar spheres, talc, triethyl citrate, titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 30 °C in blister packs.

6.5. Nature and contents of container

CYMGEN capsules are supplied in blister packs composed of cold-form aluminium laminate on one side and aluminium foil on the other side and packed in cartons of 28 capsules.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS:

CYMGEN 30: 41/1.2/1029

CYMGEN 60: 41/1.2/1030

9. DATE OF FIRST AUTHORISATION

17 April 2009

10. DATE OF REVISION OF TEXT

01 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Namibia: NS3
CYMGEN 30: 16/1.2/0201
CYMGEN 60: 16/1.2/0202

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