Hull and East Riding Prescribing Committee

Prescribing Information for Duloxetine in Depressive Illness

APPROVAL PROCESS

<table>
<thead>
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<tbody>
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<td>HMHTT DTC</td>
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1. BACKGROUND

This document aims to provide information to GPs on the prescribing of duloxetine by GPs. The Hull and East Riding Prescribing Committee has advised that Duloxetine is a green drug but should only be initiated following consultation with a specialist. This document is not a prescribing framework.

2. INDICATION COVERED BY THIS GUIDELINE

This guideline relates to the use of duloxetine (Cymbalta®) for the treatment of major depressive episodes

Duloxetine (Cymbalta®) is also licensed for the treatment of diabetic peripheral neuropathic pain in adults and generalised anxiety disorder

Care must be taken as another preparation of duloxetine that is licensed for the treatment of moderate to severe stress incontinence is available (Yentreve®)

Current NICE guidance on the management of depression in primary and secondary care suggests that duloxetine may be considered for patients who have failed two adequate trials of alternative antidepressants when initiated under the supervision by a specialist.

3. DOSE

The starting and recommended maintenance dose is 60mg once daily, with or without food. Dosages above 60mg once daily, up to a maximum dose of 120mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations. Therapeutic response is usually seen after 2-4 weeks of treatment.
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with CYMBALTA 120 mg per day for which data are limited.

**Duloxetine is not recommended for the treatment of depression in children and adolescents under the age of 18 years**

4. **DURATION OF TREATMENT**

The duration of treatment will vary according to the individual patient and their circumstances. After consolidation of the antidepressant response, it is recommended to continue treatment for a minimum of 6 months, in order to avoid relapse. Some patients require longer periods of treatment; advice can be sought from NICE guidance of depression.

5. **ADVERSE EFFECTS**

The following side effects have been observed with duloxetine:

**Very common**- headache, somnolence, dizziness, nausea, dry mouth

**Common**- weight decreased, palpitations, paraesthesia, blurred vision, tinnitus, yawning, constipation, diarrhoea vomiting, dyspepsia, flatulence, sweating increased rash, musculoskeletal pain, muscle tightness and spasm, decreased appetite, flushing, fatigue, abdominal pain, erectile dysfunction, insomnia, agitation, decreased libido, anxiety, abnormal orgasm, abnormal dreams,

**Uncommon**- weight increase, CPK increase, tachycardia, SV arrhythmia mainly AF, myoclonus, nervousness, disturbance in attention, lethargy, dysgeusia, dyskinesia, restless legs, poor sleep quality, mydriasis, visual disturbance, vertigo ear pain, throat tightness, epistaxis, gastroenteritis, eructation, gastritis, Urinary retention, dysuria, urinary hesitation, nocturia, polyuria, urine flow decreased, night sweats, urticaria, contact dermatitis, cold sweats, photosensitivity, increased bruising, muscle twitching, hyperglycaemia, laryngitis, increased blood pressure, cold extremities, orthostatic hypotension, syncope, abnormal feeling, feeling cold, thirst, chills, malaise, feeling hot, gait disturbance,
elevated liver enzymes (ALT, AST, ALK Phos), hepatitis, acute liver injury, ejaculation problems, sexual dysfunction, gynaecological haemorrhage, sleep disorder, bruxism, disorientation, apathy

Rare: increased cholesterol, convulsion, glaucoma, stomatitis, breath odour, haematochezia, abnormal urine odour, trismus, hypothyroidism, hyponatraemia, dehydration, hypersensitivity, anaphylaxis, menopausal symptoms, mania, hallucinations, aggression and anger,

**Special warnings**

*Mania and seizures:* use with caution in patients with a history of mania or a diagnosis of bipolar disorder and/or seizures.

*Mydriasis:* Mydriasis has been reported in association with duloxetine; therefore, caution should be used when prescribing for patients with increased intra-ocular pressure or those at risk of acute narrow-angle glaucoma.

*Blood pressure:* In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate.

*Renal impairment:* Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30ml/min).

*Use with antidepressants:* Caution should be exercised when using in combination with antidepressants. In particular, the combination with selective, reversible MAOIs is not recommended.

*St John's Wort:* Undesirable effects may be more common during concomitant treatment with preparations containing St John's Wort (*Hypericum perforatum*).

*Suicide:* Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Close supervision of high-risk patients should accompany drug therapy.
**Haemorrhage:** There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with selective serotonin reuptake inhibitors (SSRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

**Hyponatraemia:** Hyponatraemia has been reported rarely, predominantly in the elderly, when administering duloxetine and other drugs of the same pharmacodynamic class.

**Pregnancy and lactation:** There are no data on the use of duloxetine in pregnant women. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. The use of duloxetine while breast-feeding is not recommended.

**Discontinuation of treatment:** Some patients may experience symptoms on discontinuation of duloxetine, particularly if treatment is stopped abruptly.

**Medicinal products containing duloxetine:** Duloxetine is used under different trademarks in several indications (major depressive episodes, as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

### 6. INTERACTIONS

**CNS medicinal products:** The risk of using duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated with exception of the in the cases noted. Caution is advised when duloxetine is taken in combination with other centrally acting medicinal products and substances including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

**Monoamine oxidase inhibitors (MAOIs):** Due to the risk of serotonin syndrome, duloxetine should not be used in combination with non-selective, irreversible monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days
should be allowed after stopping Duloxetine before starting an MAOI.

*Selective reversible monoamine oxidase inhibitors (RIMAs):* On use with RIMAs, like moclobemide, the risk of serotonin syndrome is lower but concomitant use is not recommended.

*Serotonin syndrome:* In rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g., paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if Duloxetine is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John’s Wort (*Hypericum perforatum*), venlafaxine, or triptans, tramadol, pethidine, and tryptophan.

**Effect of Duloxetine on Other Drugs**

*Medicinal products metabolised by CYP1A2:* The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60mg twice daily)

*Medicinal products metabolised by CYP2D6:* Caution is advised if Duloxetine is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants, flecainide, propafenone and metoprolol)

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin

**Effects of Other Drugs on Duloxetine**

*Inhibitors of CYP1A2:* Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC₀₋₆-fold. Therefore, duloxetine should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine
Inducers of CYP1A2: Population pharmacokinetic studies have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

Always check with BNF or Data Sheet (available electronically at www.bnf.org.uk and www.medicines.org.uk)

7. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of Duloxetine with non-selective, irreversible monoamine oxidase inhibitors (MAOIs)

Liver disease resulting in hepatic impairment.

Severe renal impairment (creatinine clearance <30ml/min). Uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis

Concomitant use with fluvoxamine, ciprofloxacin, or enoxacine (i.e., potent CYP1A2 inhibitors), since the combination results in elevated plasma concentrations of duloxetine.

8. MONITORING

For patients with heart disease or known hypertension blood pressure monitoring is recommended.

It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery. As depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, until significant remission occurs patients should be closely monitored in the early stages of treatment.
9. INFORMATION TO PATIENT

Controlled studies indicate that duloxetine does not impair psychomotor performance, cognitive function, or memory, it may be associated with sedation. Patients should be cautioned about their ability to drive a car or operate hazardous machinery.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Patients should be advised that all antidepressants work slowly and that improvement can be expected over a period of weeks. Some improvement may be noticeable after two to three weeks but the full antidepressant effects are usually felt after about four to six weeks.

Patients should be advised that although duloxetine is not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if duloxetine is stopped abruptly.
## 10. RESPONSIBILITIES OF CLINICIANS INVOLVED

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<tr>
<th>Stage of Treatment</th>
<th>Hospital Specialist</th>
<th>General Practitioner</th>
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<tbody>
<tr>
<td>Initiation</td>
<td>-Selection of suitable patient when required</td>
<td>-Liaise with Community Psychiatric Nurses (CPNs) and the specialist.</td>
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<td>-Provide verbal and written treatment information to</td>
<td>-Initiation of prescribing and titration of dose, with advice of specialist when</td>
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<tr>
<td></td>
<td>patient when appropriate</td>
<td>appropriate</td>
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<td></td>
<td></td>
<td>-To take over prescribing responsibility from specialist when appropriate</td>
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<tr>
<td>Monitoring of</td>
<td>-Provide support to GP</td>
<td>-Monitor response to treatment and refer to consultant if deterioration in patient’s</td>
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<tr>
<td>treatment</td>
<td>-Advise on dose alterations when necessary.</td>
<td>mental state occurs.</td>
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<tr>
<td></td>
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<td>-Liaise with CPN and the specialist when required.</td>
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<tr>
<td>Termination of</td>
<td>-Advising the GP when duloxetine should be discontinued</td>
<td>-Co-operating with the Specialist during the discontinuation phase</td>
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<tr>
<td>treatment</td>
<td>for patients receiving long-term treatment.</td>
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<tr>
<td></td>
<td>-Provide necessary supervision and support during the</td>
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<td>discontinuation phase</td>
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