EU Risk Management Plan (Version 14.0)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

Approval Date: 16-Jun-2020 GMT

EU Risk Management Plan for Duloxetine

RMP version to be assessed as part of the application: 14

Data lock point for this RMP: 31 March 2020

Date of final sign off: See cover page

Rationale for submitting an updated RMP:

To support the submission of a Type II variation to address the commitment reflected in the RMP related to the submission of the Final Study Report for F1J-MC-B034 Cymbalta Pregnancy Registry in Q2 2020.

Summary of significant changes in this RMP:

- Removal of F1J-MC-B034 Cymbalta Pregnancy Registry as Category 3 study from the Pharmacovigilance Plan where it was included as an additional pharmacovigilance activity, as the study status has changed to Complete.
- Removal of "Prospective data about potential risks of exposure to duloxetine during Pregnancy" from the list of missing information as the study report for Study B034 is submitted.
- References to the medicinal product Xeristar are removed from the RMP Part I: Product Overview, Part II: Safety Specification and Part VI: Summary of the Risk Management plan, as its Marketing Authorisation was transferred to Esteve Pharmaceuticals S.A. on the 28 February 2020, being effective from the 03 April 2020.

Other RMP versions under evaluation

Not applicable.

Details of the currently approved RMP

Version number: 13.0

Approved with procedure: EMEA/H/C/WS1527/G

Date of approval (opinion date): 25/07/2019

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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Part I: Products Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Duloxetine
Pharmacotherapeutic group(s) (ATC Code)	N06AX21
Marketing Authorisation Holder	Eli Lilly Nederland B.V
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Cymbalta, Yentreve and Duloxetine Lilly

Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Thiophenepropanamine
	Summary of mode of action: Selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) weakly inhibits dopamine reuptake.
	Important information about its composition: The drug product is composed of duloxetine hydrochloride and the inactive ingredients ammonium hydroxide reagent, hydroxypropyl methylcellulose (E-5), hydroxypropyl methylcellulose acetate succinate, purified water, sucrose, sugar spheres (nonpareil beads #30 to 35 mesh), talc (talc extra fine), triethyl citrate, and colour mixture white DDB8257W.
Hyperlink to the Product Information	Cymbalta: https://www.ema.europa.eu/en/documents/product-information/cymbalta-epar-product-information_en.pdf Yentreve: https://www.ema.europa.eu/en/documents/product-information/yentreve-epar-product-information_en.pdf Duloxetine Lilly: https://www.ema.europa.eu/en/documents/product-information/duloxetine-lilly-epar-product-information_en.pdf
Indication(s) in the EEA	**Current:** Major Depressive Disorder (MDD) Diabetic Peripheral Neuropathic Pain (DPNP) Generalised Anxiety Disorder (GAD) Stress Urinary Incontinence (SUI)
	Proposed: Not applicable
Dosage in the EEA	**Current:** **MDD:** The starting and recommended maintenance dose is 60 mg daily with or without food. **GAD:** The recommended starting dose in patients with GAD is 30 mg once daily with or without food. In patients with insufficient response, the dose should be increased to 60 mg. **DPNP:** The starting and recommended maintenance dose is 60 mg daily with or without food. **SUI:** The recommended dose is 40 mg twice daily without regard to meals.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Each capsule of enteric-coated pellets contains duloxetine hydrochloride equivalent to 20, 30, 40, or 60 mg of duloxetine.
	Proposed: Not applicable

Product Overview

Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; EU = European Union; INN = International Nonproprietary Names; RMP = risk management plan.

Part II: Safety Specification

Module SI - Epidemiology of the Indications and Target Populations

SI.1 Major Depressive Disorder (Cymbalta/Duloxetine Lilly)

SI.1.1 Incidence

In the Netherlands, incidence of major depressive disorder (MDD) in a nationally representative sample of adults aged 18 to 64 years of age (n=5303) was 1.58 per 100 person-years over the mean 3-year follow-up in the study (2007-2009 Wave 1; 2010-2012 Wave 2) (de Graaf et al. 2013). A population-based study conducted in the United Kingdom (UK), The Health Improvement Network (THIN), with information from general practices, found the combined incidence of diagnosed depression to be 24.8 per 1000 person-years at risk, or a mean annual incidence of 2.5%, between 1996 and 2006 (Rait et al. 2009).

SI.1.2 Prevalence

In the DEPRES (Depression Research in European Society) study, the first large pan-European survey of depression in the community, with a total of 78 463 adults across 6 countries participating, the 6-month prevalence of MDD ranged from 3.8% (Germany) to 9.9% (UK) (Lépine et al. 1997). The prevalence of major depressive episode in an adult French cohort (n=36 105) aged 18+ was 11.0% (Leray et al. 2011).

SI.1.3 Demographics of the Population

Age and Gender

According to a population-based study conducted in the UK, demographic trends in MDD incidence include the frequency of recorded symptoms being twice as common in females as compared to males. Additionally, the highest rate of depressive symptoms occurred in adult patients between the ages of 25 and 44 years, and in patients who were classified as having a lower socioeconomic status (most deprived group) (Rait et al. 2009).

Risk Factors for the Disease

Sriwattanakomen et al. (2010) provides a list of many known risk factors for depression. Sociodemographic and psychosocial risk factors include gender, educational attainment in years, household income, bereavement in the past year, living alone, being a caregiver, and interpersonal support. Medical and health-related risk factors include presence of functional disability, chronic pain, and obesity. Psychiatric risk factors include history of MDD, chronic insomnia, current anxiety disorder, and history of substance abuse. Cognitive risk factors included scores on tests of executive function and overall cognitive status.

In a meta-analysis that examined risk factors for depression among elderly community subjects, bereavement, sleep disturbance, disability, prior depression, and female gender were identified as important risk factors, despite methodological limitations of the studies (Cole and Dendukuri 2003).

SI.1.4 Main Existing Treatment Options

Relevant classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs) (Hale 1997; Langworth et al. 2006; NICE 2010). These drugs are generally accepted to be effective antidepressants with a favourable safety profile relative to older agents such as tricyclic antidepressants and monoamine oxidase inhibitors. Commonly prescribed SSRIs include fluoxetine, sertraline, escitalopram, paroxetine, and citalopram. The SNRI class includes venlafaxine, milnacipran, and duloxetine. The NRI class of medication includes only reboxetine, which is approved for severe to very severe depression. An additional agent includes mirtazapine, which belongs to the NaSSA class. Overall, definitive evidence with regard to relative effectiveness among agents in these classes is lacking. When pharmacological treatment for MDD is required, SSRIs are generally considered first-line treatment (NICE 2010).

Bupropion is an antidepressant of the aminoketone class that weakly inhibits dopamine and norepinephrine reuptake and has demonstrated efficacy in the treatment of MDD (Moreira 2011; Wellbutrin package insert, 2013).

SI.1.5 Natural History of Major Depressive Disorder Including Mortality and Morbidity

Natural History: The course of MDD has considerable variation in remission and chronicity. Higher symptom severity, psychiatric comorbidity, and a history of childhood trauma predict a less favourable course. In a review of population-based studies, the mean episode duration varies from 13 to 30 weeks and 70 to 90% of subjects recover within a year. Outpatient settings have less favourable outcomes with >50% of patients still having MDD after 2 years. Even in MDD remission, residual symptoms and impairment can still exist and the chance of recurrence is high with about 80% of patients experiencing a lifetime recurrence. Major depressive disorder is also associated with an increased risk of developing conditions such as diabetes mellitus, heart disease, and stroke (Otte et al. 2016).

Morbidity: According to a review conducted by Rosenthal (2003), comorbid disorders such as cardiovascular (CV) disease, diabetes, and irritable bowel syndrome are commonly associated with major depression. Specifically, studies have shown that depression may not only exacerbate these issues but could also be an independent risk factor for the development of these comorbidities and further worsen their prognoses (Rosenthal 2003).

Mortality: One study found that patients with MDD are almost 20 times more likely to die by suicide compared to the general population (standardised mortality ratio: 19.7; 95% confidence interval [CI]: 12.2-32.0) (Chesney et al. 2014). Cuijpers et al. (2014) conducted a comprehensive meta-analysis of excess mortality in depression compared to the general population among community samples and various diseases. Of the 293 included studies, 115 were from European countries. The unadjusted relative risk of excess mortality in depressed compared to non-depressed participants from European countries was 1.74 (95% CI: 1.62-1.87, I2=84, p<0.001). After adjusting for publication bias, the overall relative risk globally was 1.52 (95% CI: 1.45-1.59).

SI.1.6 Important Co-morbidities

Alcohol abuse and/or dependence: The multi-site longitudinal cohort study in the Netherlands (NESDA) found the frequency of comorbid alcohol dependence/abuse among MDD patients (n=1115) to be 32.2% (Schuch et al. 2014). Among adult MDD patients (ages 20-65; n=1105) in a cohort sample derived from the Leiden Routine Outcome Monitoring Study in the Netherlands, the frequency of comorbid alcohol abuse/dependence was approximately 7.23% (van Noorden et al. 2011).

Drug abuse and/or dependence: Among adult MDD patients (aged 20 to 65 years; n=1105) from a cohort sample derived from the Leiden Routine Outcome Monitoring Study in the Netherlands, the frequency of comorbid drug abuse/dependence was approximately 4.4% (van Noorden et al. 2011).

Concomitant medications in the target population: In a sample of 244 859 patients with depression and an antidepressant medication from the Veterans Administration mental health settings in 2002 (Valenstein et al. 2006):

- Approximately 53 807 (22%) of depressed patients treated in mental health settings received antidepressant augmentation, with approximately 10 542 (4%) receiving >1 augmenting agent during the year.
- The most popular augmenting agents were a second antidepressant (26 739 [11%]) and a second-generation antipsychotic (17 797 [7%]). Approximately 4% (9053 patients) received augmentation with anticonvulsants and 11 054 (5%) received other augmenting agents.
- Only 1106 patients (0.5%) received augmentation with lithium.
- Bupropion appeared in 20 279 (38%) of all antidepressant-antidepressant combinations and mirtazapine appeared in 5159 (19%).
- Risperidone and olanzapine were the most frequently appearing antipsychotic agents in antidepressant-antipsychotic combinations.

SI.2 Diabetic Peripheral Neuropathic Pain (Cymbalta/Duloxetine Lilly)

SI.2.1 Incidence

A population-based analysis that utilised data from all patients who were registered at a General Practice Research Database practice in the UK between 01 January 2005 and 31 December 2010 reported an annual incidence of diabetic peripheral neuropathic pain (DPNP) of 2.8 per 10 000 population (Hall et al. 2013). A population-based study conducted in the Netherlands between 1996 and 2004 assessed neuropathic pain conditions in the general population and found the incidence of DPN to be approximately 72.3 cases per 100 000 person-years (Dieleman et al. 2008).

SI.2.2 Prevalence

Epidemiological data on the prevalence of pain related to DPNP are limited (Barrett et al. 2007); however, it has been reported that approximately 16% to 26% of patients with diabetes experience DPNP (Jensen et al. 2006). Recent population-based studies have confirmed these

findings, with Abbott et al. (2011) reporting painful diabetic neuropathy prevalences of 21.5% in type 2 diabetics (n=14 144) and 13.4% in type 1 diabetics (1333) in the UK and a neuropathic pain prevalence of 16.0% among type 1 or type 2 diabetics (n=1113) in Turkey (Erbas et al. 2011).

SI.2.3 Demographics of the Population

Age and Gender

The incidence (%) of DPNP increases with age, as reported in a UK study among DPNP patients (n=5340) as follows (Hall et al. 2013):

- Age 0 to 14: female, 0%; male, <0.1%
- Age 15 to 29: female, 0.2%; male, 0.1%
- Age 30 to 44: female, 0.8%; male, 0.9%
- Age 45 to 59: female, 3.0%; male, 3.7%
- Age 60 to 74: female, 7.0%; male, 9.2%, and
- Age ≥75: female, 8.3%; male, 10.8%.

Risk Factors for the Disease

The results of studies of risk factors for DPNP are sometimes conflicting, but age and diabetes duration have been the most frequently reported risk factors (Hartemann et al. 2011). According to Spallone et al. (2012), definite risk factors for DPNP are diabetes duration, glycaemic control, presence of other microangiopathic complications, hypertension, and smoking (the latter mainly in type 1 diabetes).

SI.2.4 Main Existing Treatment Options

Anticonvulsants are among the most commonly used therapeutic options for the management of DPNP (Wong et al. 2007). Pregabalin, which belongs to this class of medication, is approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) as well as other neuropathic pain conditions (Lyrica Summary of Medicinal Product Characteristics [SmPC] 2018).

Oral opioid analgesics have demonstrated efficacy in randomised clinical trials in patients with a variety of neuropathic pain conditions, including painful DPN, and the magnitude of pain reduction associated with opioid analgesics is at least as great as that obtained with other treatments for neuropathic pain (Dworkin et al. 2007). However, they should generally be used as second-line treatment due to side effects and risk for misuse and abuse (Dworkin et al. 2007).

SI.2.5 Natural History of Diabetic Peripheral Neuropathic Pain Including Mortality and Morbidity

Natural History: The natural history of DPN and DPNP is largely unknown because available published information is limited.

Morbidity: Morbidity associated with DPNP include those commonly associated with chronic pain such as depression and sleep disturbance and those associated with diabetes such as vascular disease (Jensen et al. 2006). Diabetic peripheral neuropathic pain can impair quality of life by

interfering with general activity, mood, mobility, work, social relations, sleep, leisure activities, and enjoyment of life (Barrett et al. 2007). Persistent neuropathic pain is associated, if not the cause of, depression, anxiety, loss of sleep, and noncompliance with treatment (Vinik et al. 2013).

Mortality: Patients with diabetes are known to have a greater risk for mortality due to conditions such as ischemic heart disease and renal failure. With respect to neuropathic pain, a study conducted among diabetic patients in the UK between 1982 and 1985 found an increased risk of mortality associated with microvascular complications such as peripheral sensory neuropathy. The authors noted that increased mortality might also be due to subsequent foot ulceration and gangrene (Coppini et al. 2000).

SI.2.6 Important Co-morbidities

The baseline diabetes and pain-related comorbidities of DPNP patients (n=11 060) enrolled in a retrospective US claims database study were as follows (Chen et al. 2011):

- CV diseases 63.4% – 70.2%
- Cerebrovascular/peripheral vascular diseases 26.1% – 32.7%
- Retinopathy 13.2% – 16.8%
- Obesity 6.2% – 8.1%
- Anxiety disorders 2.5% – 5.5%
- Low back pain 24.0% – 38.5%
- Osteoarthritis 16.8% – 25.5%
- Fibromyalgia syndrome 6.0% – 9.9%, and
- Depression 44% (D'Amato et al. 2016).

Concomitant medications in the target population: A population-based study conducted in the Netherlands found that the frequency of pain-related concomitant treatments were as follows (Dieleman et al. 2008):

- Anticonvulsant: 3.4%
- Tricyclic antidepressant: 8.4%
- SSRIs: 4.2%
- Corticosteroids: 5.4%
- Nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin: 22.9%
- Opioids: 7.1%
- Sedatives/hypnotics: 14.4%, and
- Benzodiazepines: 14.2%.

SI.3 Generalised Anxiety Disorder (Cymbalta/Duloxetine Lilly)

SI.3.1 Incidence

According to data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) among all adult Dutch patients aged 18 to 64, the incidence of generalised anxiety disorder (GAD) was determined to be 0.72 cases per 100 person-years at risk, whereas in males and females the rates were 0.45 and 0.98 cases per 100 person-years, respectively (Bijl et al. 2002).

SI.3.2 Prevalence

The European Study of the Epidemiology of Mental Disorders/Mental Health Disability (ESEMed Project), conducted in 6 European countries (Belgium, France, Germany, Italy, the Netherlands, and Spain), found the 12-month and lifetime prevalence of GAD in the adult general population to be 1.0% and 2.8%, respectively (Alonso et al. 2004).

SI.3.3 Demographics of the Population

Age and Gender

In a large retrospective longitudinal UK cohort study in adult patients with a diagnosis of GAD, 66.8% were female, and the mean age was 48.5 years (standard deviation [SD] 17.5 years) (Chollet 2013). In another Spanish study, the majority of GAD patients were female (69.4%), and the mean age was 52.8 years (SD 13.8). European studies have found that GAD prevalence increases from young adulthood through mid-50s, a pattern unlike other anxiety disorders indicating that it is typically an adult-onset disorder (Weisberg et al. 2009)

Risk Factors for the Disease

Risk factors for GAD include a family history of the condition, an increase in stress, and a history of physical and or emotional trauma. Compared to individuals without anxiety and depression, the following putative risk factors for GAD were identified in 106 German GAD patients: parental GAD, high behavioural inhibition, exposure to childhood separation events, and parental overprotection (Beesdo et al. 2010).

SI.3.4 Main Existing Treatment Options

The efficacy of SSRIs such as paroxetine and escitalopram in the treatment of GAD is well established (Paxil package insert, 2012; Goodman et al. 2005), and these agents are preferred over benzodiazepines because of the common comorbidity with depression as well as the low risk of dependence (Baldwin and Nair 2005). The SNRI venlafaxine extended release has also demonstrated efficacy in the treatment of GAD (Effexor XR package insert, 2012). When pharmacological treatment for GAD is required, some treatment guidelines have identified SSRIs as first-line treatment (NICE 2011).

Benzodiazepines are effective in alleviating anxiety symptoms rapidly in acute treatment (Rickels et al. 1983, 1997; Pollack et al. 2003); however, they are controversial for long-term treatment.

SI.3.5 Natural History of Generalised Anxiety Disorder Including Mortality and Morbidity

Natural History: Generalised anxiety disorder (GAD) is characterised by persistent and excessive worry more often than not over a span of at least 6 months. It is a long-term illness with a high likelihood of recurrence. The disease course is affected by several factors. Poor family relationships and the presence comorbid cluster C personality disorders (avoidant, dependent, and obsessive-compulsive personality disorders) are associated with less likely remission. Major depressive disorder, panic disorders, agoraphobia, and substance abuse

disorders also predict less likely recovery. Studies have shown that women are less likely to remit but also less likely to relapse once remitted (Weisberg et al. 2009). Common symptoms can include restlessness and inability to relax, fatigue, sleep disturbance, irritability, muscle tension, muscle aches, headache, chest pain, and other types of pain (Hoffman et al. 2008). Comorbidity is a common and characteristic feature of the natural progression of GAD. An estimated 80% of lifetime GAD patients will have a comorbid mood disorder during their lifetime. Depression is the most common mood disorder, and when GAD and depression occur together, patients experience increased disability and dysfunction. In 50% or more cases of GAD and comorbid depression, GAD precedes the first episode of major depression. When GAD is comorbid with other conditions, the rate of suicide increases (Ballenger et al. 2001; Lamers et al. 2011).

Morbidity: Patients who have GAD along with coexisting psychiatric illnesses have more impairment, seek more medical attention, and have a poorer response to treatment than those without coexisting illnesses (Fricchione 2004). Anxiety disorders are the cause of substantial distress and impairment to individuals who suffer from them. People with anxiety disorders have lower quality of life in work, social, and family domains as well as poorer physical and mental health than those without anxiety disorders (Olatunji et al. 2007).

Mortality: The data linking GAD with an increased risk of mortality appears to be conflicting, with some studies showing an increased risk in all-cause mortality (compared to mortality due to neoplasms, circulatory, and respiratory conditions) (Laan et al. 2011). In another study, anxiety was associated with increased all-cause mortality when adjusted for only age and gender, but in the fully adjusted model, there was a negative correlation (Mykletun et al. 2007).

SI.3.6 Important Co-morbidities

In addition to comorbid psychiatric comorbidities, persons with GAD also frequently experience comorbid physical disorders such as migraine, rheumatoid arthritis, peptic ulcer disease, diabetes, irritable bowel syndrome, coronary heart disease, hyperthyroidism, asthma, and chronic obstructive pulmonary disorder (Culpepper 2009; Hoffman et al. 2008; Chollet 2013; Ballenger et al. 2001).

Concomitant medications in the target population: In a Spanish cross-sectional study of 1871 patients with GAD, the frequencies of concomitant medications were (Garcia-Campayo et al. 2012):

- Benzodiazepines: 86.5%
- Antidepressants: 69.4%
- Antiepileptics: 49.7%.
- Acetaminophen: 8.4%
- Ibuprofen: 6%
- Tramadol: 3.1%), and
- Proton pump inhibitors: 6.9%.

SI.4 Stress Urinary Incontinence (Yentreve)

SI.4.1 Incidence

Two large cross-sectional surveys conducted among women in Norway (EPINCONT 1 and 2) found the cumulative crude incidence of stress urinary incontinence (SUI) to be 6.5% after including adult females from 2 periods of ascertainment (1995 to 1997 and 2006 to 2008) (Ebbersen et al. 2013).

Among Danish women followed for 12 years after their first birth delivery, the 12-year incidence of SUI was 30% (44 of 146) (Viktrup et al. 2006).

SI.4.2 Prevalence

A broad disparity exists among reported prevalence rates of SUI because the epidemiological definition of SUI has not been established (Luber 2004), and the definition used may vary from study to study (Minassian et al. 2008). Overall, however, SUI is generally the most prevalent type of urinary incontinence (UI) among women (Irwin et al. 2006; Temml et al. 2000). The EPIC study (Irwin et al. 2006) assessed prevalence rates of overactive bladder, UI, and other lower urinary tract symptoms among individuals (n=19,165) in Canada, Germany, Italy, Sweden, and the UK. According to this survey, the prevalence of SUI was 0.6% among men and 6.4% among women.

Studies from 2 EU member states were conducted to estimate the prevalence of SUI, and the results are summarised in Table SI.1 below:

Table SI.1. Prevalence of SUI in Belgium and Sweden

Region	Reference	N	Study Details	Prevalence of SUI
Belgium	de Ridder et al. 2013	7139	Women ≥40 years visiting a GP for any reason between February and May 2011. Mean age: 61 years.	Moderate-severe SUI =17.7%
Sweden	Gyhagen et al. 2013	5118	Primiparous women with no further births (1985-1988).	15.3%

Abbreviations: GP = general practitioner; SUI = stress urinary incontinence.

SI.4.3 Demographics of the Population

Age and Gender

Stress urinary incontinence is significantly more prevalent in females than in males (Irwin et al. 2006; Markland et al. 2011) and the prevalence of SUI increases with age. In a review of 21 studies (11 of which were conducted in Europe), the median prevalence of SUI in females peaked in the fourth decade of life. The median prevalence of significant UI (all types, including SUI) increased from the second to the eighth decades of life (Minassian et al. 2003).

Risk Factors for the Disease

Several risk factors have been identified for SUI. In a study based on National Health and Nutrition Examination Survey (NHANES) survey data (2001 to 2002) in adult women, reported age, ethnic background, and weight as significant risk factors common to mild, moderate, or

severe UI (Minassian et al. 2008). White women were at a significantly higher risk of SUI than Blacks and Hispanics. Smoking and thyroid problems were identified as additional risk factors for mild SUI. Parity was an additional risk factor for moderate or severe SUI, and previous hysterectomy and parity were identified as additional risk factors for severe SUI (Minassian et al. 2008).

SI.4.4 Main Existing Treatment Options

Nonsurgical treatment: Initial management of SUI is typically with conservative, nonsurgical treatments such as lifestyle modifications, physical therapies, behavioural therapies, and weight loss in overweight patients (Abrams et al. 2009; Lucas et al. 2018). The National Institute for Health and Care Excellence (NICE) recommends pelvic floor muscle training (PFMT) as first-line treatment. Pelvic floor muscle training is the most commonly used physical therapy treatment for women with SUI, and several randomised clinical trials have demonstrated that PMFT is more effective than no treatment (NICE 2006; Abrams et al. 2009; Dumoulin and Hay-Smith 2010; Bø 2012).

Surgery: Surgery is generally limited to severe cases that have not responded to conservative treatments. The European Association of Urology guidelines on UI state that surgical treatment of UI is usually considered after the failure of conservative therapy or drug treatment (limited to duloxetine for SUI), while the NICE guidelines on UI state that surgical treatment should be offered after conservative treatment has failed (NICE 2006; Lucas et al. 2018).

SI.4.5 Natural History of SUI Including Mortality and Morbidity

Natural History: Stress urinary incontinence is characterised by involuntary leakage on effort or exertion, or on sneezing or coughing (Luber 2004). Urinary incontinence subtypes have been reported to transition amongst one another and the general trend appears to increase the progression towards mixed UI. Since many women do not seek care during early stages and usually seek care once symptoms have advanced, there may be lost opportunity to revert progression (Minassian et al. 2017). Among women, the proportion of UI classified as SUI is generally the highest, though this proportion appears to decrease with age (Hunskaar et al. 2000). During the 4-year follow-up, SUI appeared to be more stable in severity than other subtypes in this group of women (Jahanlu and Hunskaar 2011).

Morbidity: While not life threatening, SUI can have a significant impact on the quality of a sufferer's life, including the distress it causes and avoidance of activities. Incontinence impairs sexual activity, affects social activities, can lead to isolation, and generally decreases social and psychological well-being (Monz et al. 2005). It was reported that not only UI/SUI patients are more likely to have depression and anxiety, but also depression and anxiety are known risk factors for patients to develop SUI (Felde et al. 2017).

Mortality: Data are not available in the literature.

SI.4.6 Important Co-morbidities

Comorbidities of women with SUI in an observational, postauthorisation safety study for duloxetine conducted in Germany between 2005 and 2008 were as follows (Michel et al. 2013):

- Hypertension: 54.2%
- Lipid metabolism disorder: 35.4%
- Diabetes/prediabetes: 22.6%
- Heart disease: 12.9%
- Depression: 17.0%
- Bronchopulmonary disease: 6.4%
- Neurogenic urinary hesitancy: 1.1%
- Coagulation disorder: 1.1%, and
- Liver diseases: 1.6%.

Concomitant medications in the treatment population: Concomitant medications taken by women with SUI in an observational, postauthorisation safety study for duloxetine conducted in Germany between 2005 and 2008 were as follows (Michel et al. 2013):

- Antihypertensives: 52.8%
- Hormones: 5.2%
- Anticoagulants: 7.8%
- Antidepressants: 10.8%
- Theophylline: 3.3%, and
- Sedatives: 5.4%.

The above figures relate to the co-morbidities and concomitant medications at baseline for the duloxetine treated patients; those for the comparator arm of the study were very similar.

Module SII - Nonclinical Part of the Safety Specification

SII.1 Toxicity

Duloxetine has been evaluated comprehensively in a variety of toxicology studies in laboratory animals and in vitro test systems, and no further nonclinical studies are warranted. This also takes into account the extensive postauthorisation experience of duloxetine after more than 15 years on the market and more than 100 million patient exposures.

Key issues identified following oral administration (acute or repeated dose) to rats and dogs were related to the following:

- Central nervous system (CNS): CNS effects included tremors, convulsions, emesis, mydriasis, salivation, and hyper-responsiveness. Some CNS effects have been reported in humans and are listed as adverse drug reactions (ADRs) in the SmPC (tremor, convulsions, vomiting, mydriasis, nervousness, and restlessness).
- Liver: Non-adverse effects on liver observed in repeated-dose studies included hepatic microsomal enzyme induction with corresponding increased liver weights and centrilobular hepatic hypertrophy, centrilobular fatty changes/vacuolation and phospholipidosis (Wernicke et al. 2008). Multinucleated cells without other histopathological changes (rat carcinogenicity study) underlying mechanism and clinical relevance unknown. In humans, duloxetine's most common effects on the liver are manifested by transient, self-limiting transaminase elevations. Rare events characterised as hepatocellular injury, cholestatic injury, or mixed type of hepatic injury have been reported. Hepatic effects have been subject to systematic evaluation in everyday clinical practice and are well documented in the SmPC.

Duloxetine has been tested in a battery of studies designed to test for developmental and reproductive toxicity; results are described below:

- Fertility: Fertility was not affected in male rats; effects on female rat fertility (e.g., oestrous cycle disruption) and developmental delay (e.g., depressions in live birth indices and progeny growth) occurred only at maternally toxic doses. Some effects (decreased pup survival and body weight) on offspring of rodents dosed with duloxetine were observed; the human relevance is unknown.
- Embryo foetal development: There was no evidence of teratogenicity in rats and rabbits exposed to duloxetine during gestation at doses up to 45 mg/kg/day; however, foetal weights decreased. The no-effect dose was 10 mg/kg/day.
- Prenatal and postnatal development: Duloxetine was administered to pregnant rats throughout gestation and lactation. Decreased pup survival (1 day postpartum) and body weights (at birth and during lactation) were observed. Pups exhibited behaviours consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity. There were no effects on postweaning growth and reproductive performance of the progeny. The no-effect dose was 10 mg/kg/day.

The human significance of the reproductive and developmental effects in rodents was unknown at the time of submission. However, the use of duloxetine during pregnancy has been closely monitored in the past 15 years since first authorisation, as well as subject to systematic postauthorisation study with no major safety concerns identified that would alter the risk-benefit of the drug.

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats or male mice. An increased incidence of hepatocellular adenomas and carcinomas in female mice (at a high dose of 144 mg/kg/day only) was considered secondary to hepatic microsomal enzyme induction; the no-effect dose was 50 mg/kg/day. Enzyme induction-related liver tumours are a common finding in rodents and do not appear to have direct or known human significance.

Juvenile rats were exposed to duloxetine from postnatal day (PND) 21 (weaning) through PND 90 (adult). Similar to findings in adult rats, decreased body weight and food consumption and hepatic enzyme induction and hepatocellular vacuolation were observed. There was no effect on male or female fertility. Slightly delayed (~1.5 days) sexual maturation in females was attributed to body weight effects. There was a minor, transient delay in learning a complex task in adulthood. There were no effects on motor activity and auditory startle habituation. The no-effect-level was 20 mg/kg/day. The effects observed in juvenile rats have not given rise to any safety signals or safety concerns in human use, however, use in children is not recommended.

SII.2 Safety Pharmacology

A battery of safety pharmacology studies was conducted with duloxetine; key results are described below.

- CV and Pulmonary: At the maximum clinically achieved unbound plasma concentration of duloxetine (90 nM or 30 ng/mL), duloxetine had no effect on human cardiac ion channels. Cardiovascular function was not significantly altered following oral administration of 7 mg/kg or 20 mg/kg in the conscious rat. In the anesthetised dog, significant CV effects (e.g., increases in mean pulmonary arterial and capillary wedge pressures, pulmonary vascular resistance, and heart rate) were observed at intravenous doses of ≥2 mg/kg, and intravenous doses of ≥0.4 mg/kg stimulated respiratory rate. However, in conscious dogs, intravenous (2 mg/kg) or oral (10 mg/kg) administration had no effect on pulmonary or systemic arterial pressure or on heart rate.
- CNS: In a safety pharmacology study in mice, duloxetine did not adversely affect the CNS functions at acute oral doses of ≤3 mg/kg. Multiple (5-day) oral administration of duloxetine in mice resulted in tolerance to its adrenergic activity, depressed CNS activity (as evaluated using hexobarbital-induced sleep) and enhanced anticonvulsive properties.
- GI motility in mice was not affected at oral doses of up to 30 mg/kg.
- An increase in sodium excretion was the only effect on renal function in rats observed at 3 mg/kg.
- Immune functions in mice were unaltered at an oral dose of ≤130 mg/kg.

Potential secondary pharmacologic reactions of duloxetine at clinical doses would appear to be limited to increases in pulmonary pressure, pulmonary vascular resistance, and respiratory rate, effects that are attributable to the known actions of norepinephrine and serotonin (Brunner and Gross 1979; Garattini and Valzelli 1965; Weiner 1985).

SII.3 Other Toxicity-Related Information or Data

Not applicable.

Module SIII - Clinical Trial Exposure

Approximately 37 369 patients have been exposed to duloxetine in studies spanning over 20 years.

Table SIII.1. Duration of Exposure, Adult Population

Cumulative for all indications (person-time), All Duloxetine Exposures[a]		
Duration of exposure, days	**Patients** N=37 369	**Person-Time (Years)[b]**
>0	36 934	16 561.17
≥30	31 276	16 340.45
≥90	17 158	13 944.77
≥183	10 035	11 542.44
Total	36 934	16 561.17
Major Depressive Disorder, All Duloxetine Exposures[a]		
Duration of exposure, days	**Patients** N=15 144	**Person-Time (Years)[b]**
>0	14 859	4563.74
≥30	12 254	4464.96
≥90	4341	3187.03
≥183	2687	2636.34
Total	14 859	4563.74
Diabetic Peripheral Neuropathic Pain, All Duloxetine Exposures[a]		
Duration of exposure, days	**Patients** N=3420	**Person-Time (Years)[b]**
>0	3370	1691.83
≥30	2877	1676.85
≥90	1885	1484.02
≥183	1167	1272.29
Total	3370	1691.83
Generalised Anxiety Disorder, All Duloxetine Exposures[a]		
Duration of exposure, days	**Patients** N=2060	**Person-Time (Years)[b]**
>0	2041	637.69
≥30	1679	625.97
≥90	759	444.10
≥183	357	281.70
Total	2041	637.69
Stress Urinary Incontinence/Lower Urinary Tract Disorders, All Duloxetine Exposures[a]		
Duration of exposure, days	**Patients** N=11 861	**Person-Time (Years)[b]**
>0	11 821	7620.98
≥30	10 192	7544.32
≥90	7184	7062.58
≥183	4509	6097.90
Total	11 821	7620.98

Abbreviation: N = number of duloxetine patients.

[a] All duloxetine exposures refers to all patients exposed to duloxetine in either placebo-controlled or open-label trials.

[b] Patient-years calculated as total exposure days / 365.25.
Source: /lillyce/prd/ly248686/q32017safe/output/fqexpr11.rtf.

Table SIII.2. Duration of Exposure, Children/Adolescents

Cumulative for all indications (person-time), All Duloxetine Exposures[a,b]		
Duration of Exposure	**Patients (N=988) Randomised (n=987)**	**Person-time (Years)[c]**
>0 days	987	421.36
≥30 days	887	417.14
≥90 days	736	392.95
≥183 days	426	268.09
Total	987	421.36
Major Depressive Disorder, All Duloxetine Exposures[a,b]		
Duration of Exposure	**Patients (N=581) Randomised (n=580)**	**Person-time (Years)[c]**
>0 days	580	247.78
≥30 days	508	244.69
≥90 days	413	229.47
≥183 days	250	160.01
Total	580	247.78
Generalised Anxiety Disorder, All Duloxetine Exposures[a,b]		
Duration of Exposure	**Patients (N=241)**	**Person-time (Years)[c]**
>0 days	241	88.49
≥30 days	223	87.69
≥90 days	187	81.94
≥183 days	83	45.23
Total	241	88.49

Abbreviations: GAD = generalised anxiety disorder; N = number of duloxetine patients; n = number of patients randomised.

[a] All duloxetine exposures refers to all patients exposed to duloxetine in either placebo-controlled or open-label trials for the specified indication.

[b] Nine patients from a site with major quality issues in the GAD Study F1J-MC-HMGI were excluded from the analyses.

[c] Patient-years calculated as total exposure days / 365.25.

Source: /lillyce/prd/ly248686/q317safe_peds/output/fqexpr11.rtf

Table SIII.3. Age Group and Gender

All Indications, All Duloxetine Exposures[a]				
Age group (Years) N=988[b]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
7-11	183	159	74.65	63.58
12-17	252	393	109.32	173.81
Total	435	552	183.97	237.39
Age group (Years) N=37 369[c]	**Patients**		**Person-Time (Years)**	
	M	**F**	**M**	**F**
>18 to <65	6845	24 285	2437.89	11 461.37
≥65 to <75	1261	3520	460.42	1658.27
≥75to <85	358	976	105.00	411.20
≥85	14	70	4.43	21.32
Total	8478	28 851	3007.74	13 552.16
Major Depressive Disorder, All Duloxetine Exposures[a]				
Age group (Years) N=581[b]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
7-11	126	104	53.89	43.69
12-17	157	193	70.16	80.05
Total	283	297	124.05	123.74
Age group (Years) N=15 144[c]	**Patients**		**Person-Time (Years)[d]**	
Years	**M**	**F**	**M**	**F**
≥18 to <65	4141	9479	1238.49	2902.75
≥65 to <75	365	770	103.07	225.65
≥75to <85	107	233	27.80	57.49
≥85	4	25	0.61	6.63
Total	4617	10 507	1369.97	3192.52
Diabetic Peripheral Neuropathic Pain, All Duloxetine Exposures[a]				
Age group (Years) N=3420[c]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
≥18 to <65	1225	938	696.00	467.47
≥65 to <75	566	412	246.68	186.62
≥75to <85	154	108	53.28	38.15
≥85	3	0	2.86	0
Total	1948	1458	998.82	692.24

Generalised Anxiety Disorder, All Duloxetine Exposures[a]				
Age group (Years) N=241[b]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
7-11	57	55	20.76	19.90
12-17	55	74	19.98	27.85
Total	112	129	40.74	47.75
Age group (Years) N=2060[c]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
≥18 to <65	707	1098	224.07	353.27
≥65 to <75	58	134	16.23	31.36
≥75to <85	13	39	2.40	9.85
≥85	1	2	0.23	0.28
Total	779	1273	242.93	394.76
Stress Urinary Incontinence/Lower Urinary Tract Disorders, All Duloxetine Exposures[a]				
Age group (Years) N= 11 861[c]	**Patients**		**Person-Time (Years)[d]**	
	M	**F**	**M**	**F**
≥18 to <65	42	9649	4.68	6350.42
≥65 to <75	20	1638	2.34	996.61
≥75to <85	10	466	0.84	253.27
≥85	2	34	0.18	12.64
Total	74	11 787	8.04	7612.94

Abbreviations: DLX = duloxetine; F = female; GAD = generalised anxiety disorder; M = male; N = number of duloxetine patients within each age/gender group.

[a] All duloxetine exposures refer to all patients exposed to duloxetine in either placebo-controlled or open-label trials.

[b] Nine patients from a site with major quality issues in the GAD Study F1J-MC-HMGI were excluded from the analyses.

[c] Eleven subjects from all placebo-controlled DLX arm counts and 39 subjects from all DLX exposures counts are not included on this analysis because of missing age and/or gender and/or study drug exposure data.

[d] Patient-years calculated as total exposure days / 365.25.

Sources: /lillyce/prd/ly248686/q32017safe/output/fqexpr51.rtf;
lillyce/prd/ly248686/q317safe_peds/output/fqexpr41.rtf.

Table SIII.4. Duloxetine Dose, Adult Population[a]

Dose of exposure QD All Indications, All Duloxetine Exposures[b-g]	**Patients**	**Person-Time (Years)[h]**
≤30 mg	2463	437.18
40 mg	777	197.26
60 mg	14 761	3807.85
80 mg	11 807	7757.01
90 mg	1242	640.81
120 mg	5564	3281.72
Unknown	755	439.34
Total	37 369	16 561.17
Dose of exposure QD Major Depressive Disorder, All Duloxetine Exposures[b-d,f,g]	**Patients**	**Person-Time (Years)[h]**
≤30 mg	962	225.80
40 mg	218	24.65
60 mg	9652	2110.54
80 mg	979	433.81
120 mg	2360	1272.47
Unknown	200	66.54
Total	14 371	4133.81
Dose of exposure QD Diabetic Peripheral Neuropathic Pain, All Duloxetine Exposures[b-d,f,g]	**Patients**	**Person-Time (Years)[h]**
≤30 mg	411	69.73
40 mg	167	86.85
60 mg	1362	412.17
120 mg	1273	1005.63
Unknown	207	117.45
Total	3420	1691.83
Dose of exposure QD Generalised Anxiety Disorder, All Duloxetine Exposures[b-g]	**Patients**	**Person-Time (Years)[h]**
≤30 mg	306	28.05
60 mg	719	205.16
90 mg	404	186.65
120 mg	614	215.44
Unknown	17	2.39
Total	2060	637.69

Duloxetine Dose, Adult Population[a]

Dose of exposure QD Stress Urinary Incontinence/Lower Urinary Tract Disorders, All Duloxetine Exposures[b,c,f,g]	Patients	Person-Time (Years)[h]
≤30 mg	406	52.89
40 mg	392	85.76
80 mg	10 828	7323.21
120 mg	167	125.46
Unknown	68	33.65
Total	11 861	7620.97

Abbreviations: DLX = duloxetine; QD = once daily dosing.

[a] If a patient took 2 different doses for the same number of days, the higher of the 2 doses was chosen to be the modal dose.

[b] All duloxetine exposures refer to all patients exposed to duloxetine in either placebo-controlled or open-label trials.

[c] DLX≤30 QD includes patients on DLX 5 mg/day, 10 mg/day, 20 mg/day, and 30 mg/day.

[d] DLX60 QD includes patients on DLX 60 mg/day and patients on DLX 60 mg + selective serotonin reuptake inhibitor.

[e] DLX90 QD includes patients on DLX 90 mg/day and DLX 100 mg/day.

[f] DLX120 QD includes patients on DLX 120 mg/day and DLX 160 mg/day.

[g] Unknown includes patients on DLX Taper and DLX3060 as well.

[h] Patient-years calculated as total exposure days / 365.25, and total exposure days for a specific modal dose group are the total exposures for the whole treatment period.

Source: /lillyce/prd/ly248686/q32017safe/output/fqexpr31.rtf.

Table SIII.5. Duloxetine Dose, Children/Adolescents[a,b]

Dose of exposure, All Indications, All Duloxetine Exposures[c]	**Patients**	**Person-Time (Years)[d]**
20 mg	2	0.18
30 mg	231	60.53
60 mg	431	193.31
90 mg	116	54.10
120 mg	206	113.20
Total	986	421.32
Dose of exposure, Major Depressive Disorder, All Duloxetine Exposures[c]	**Patients**	**Person-Time (Years)[d]**
20 mg	2	0.18
30 mg	114	16.23
60 mg	202	88.22
90 mg	77	38.46
120 mg	184	104.65
Total	579	247.74
Dose of exposure, Generalised Anxiety Disorder, All Duloxetine Exposures[c]	**Patients**	**Person-Time (Years)[d]**
30 mg	66	20.55
60 mg	114	43.76
90 mg	39	15.64
120 mg	22	8.54
Total	241	88.49

Abbreviation: GAD = generalised anxiety disorder.

[a] If a patient took 2 different doses for the same number of days, the higher of the 2 doses was chosen to be the modal dose.

[b] Nine patients from a site with major quality issues in the GAD Study F1J-MC-HMGI were excluded from the analyses.

[c] All duloxetine exposures refer to all patients exposed to duloxetine in either placebo-controlled or open-label trials.

[d] Patient-years calculated as total exposure days / 365.25, and total exposure days for a specific modal dose group are the total exposures for the whole treatment period.

Source: /lillyce/prd/ly248686/q317safe_peds/output/fqexpr31.rtf.

Table SIII.6. Ethnic Origin, Adult Population

Ethnic Origin All Indications, All Duloxetine Exposures[a]	**Patients**	**Person-Time (Years)[b]**
American Indian or Alaskan Native	142	30.32
Asian	3382	1367.32
Black or African American	1651	545.83
Multiple	22	3.65
Native Hawaiian or other Pacific Islander	8	1.03
Other	3003	1449.70
White	26 509	11 764.13
Missing	2652	1399.20
Total	37 369	16 561.18
Ethnic Origin Major Depressive Disorder, All Duloxetine Exposures[a]	**Patients**	**Person-Time (Years)[b]**
American Indian or Alaskan Native	44	7.85
Asian	781	123.84
Black or African American	769	176.83
Multiple	9	1.56
Native Hawaiian or other Pacific Islander	4	0.79
Other	1399	602.18
White	12 134	3650.57
Missing	4	0.11
Total	15 144	4563.73
Ethnic Origin Diabetic Peripheral Neuropathic Pain, All Duloxetine Exposures[a]	**Patients**	**Person-Time (Years)[b]**
American Indian or Alaskan Native	53	8.53
Asian	942	437.01
Black or African American	76	30.86
Multiple	6	0.88
Native Hawaiian or other Pacific Islander	3	0.16
Other	245	127.03
White	2095	1087.36
Missing	0	0
Total	3420	1691.83

Ethnic Origin, Adult Population

Ethnic Origin Generalised Anxiety Disorder, All Duloxetine Exposures[a]	**Patients**	**Person-Time (Years)[b]**
American Indian or Alaskan Native	18	3.09
Asian	163	43.90
Black or African American	80	17.18
Multiple	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	173	48.82
White	1625	524.48
Missing	1	0.23
Total	2060	637.7
Ethnic Origin Stress Urinary Incontinence/ Lower Urinary Tract Disorder, All Duloxetine Exposures[a]	**Patients**	**Person-Time (Years)[b]**
American Indian or Alaskan Native	0	0.00
Asian	216	68.36
Black or African American	559	275.09
Multiple	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	857	505.38
White	7583	5373.75
Missing	2646	1398.40
Total	11 861	7620.98

[a] All duloxetine exposures refer to all patients exposed to duloxetine in either placebo-controlled or open-label trials.

[b] Patient-years calculated as total exposure days / 365.25.

Source: /lillyce/prd/ly248686/q32017safe/output/fqexpr21.rtf.

Table SIII.7. Ethnic Origin, Children/Adolescent

Ethnic Origin All Indications, All Duloxetine Exposures[a,b]	**Patients** (N=988)	**Person-Time (Years)[c]**
American Indian or Alaskan Native	68	30.37
Asian	15	7.11
Black or African American	134	50.09
Multiple	49	16.90
Native Hawaiian or other Pacific Islander	2	0.56
Other	11	5.86
White	688	301.82
Missing	20	8.64
Total	987	421.35
Ethnic Origin Major Depressive Disorder, All Duloxetine Exposures[a,b]	**Patients** (N=581)	**Person-Time (Years)[c]**
American Indian or Alaskan Native	56	24.83
Asian	2	0.25
Black or African American	107	38.19
Multiple	26	8.27
Native Hawaiian or other Pacific Islander	1	0.08
Other	11	5.86
White	358	162.42
Missing	19	7.89
Total	580	247.79
Ethnic Origin Generalised Anxiety Disorder, All Duloxetine Exposures[a,b]	**Patients** (N=241)	**Person-Time (Years)[c]**
American Indian or Alaskan Native	11	4.79
Asian	2	0.88
Black or African American	15	4.85
Multiple	14	4.50
Native Hawaiian or other Pacific Islander	0	0
Other	0	0
White	199	73.46
Missing	0	0
Total	241	88.48

Abbreviations: GAD = generalised anxiety disorder; N = number of duloxetine patients.

[a] All duloxetine exposures refer to all patients exposed to duloxetine in either placebo-controlled or open-label trials for the specified indication.

[b] Nine patients from a site with major quality issues in the GAD Study F1J-MC-HMGI were excluded from the analyses.

[c] Patient-years calculated as total exposure days / 365.25.

Source: /lillyce/prd/ly248686/q317safe_peds/output/fqexpr21.rtf.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Given that duloxetine has been on the market since August 2004 and has been subject to postmarketing exposures in excess of 100 million patients, the exclusion criteria used in the original clinical trial development programme are subsequently no longer considered applicable to determine potential safety concerns. This is due to limitations of the clinical trial programme and therefore not described in this section. The only exclusion criteria deemed relevant to this section is patients who were pregnant as this was subject to additional pharmacovigilance (PV) activity.

Patients who are pregnant

Reasons for exclusion: This is a standard exclusion criterion in any clinical research development programme for a new active substance to ensure safety and minimise risk in a research setting.

Is it included as missing information: No.

Rationale: No longer applicable as the additional PV activities are completed.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme for duloxetine was unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, as the product has now been on the market since 2004 and subject to in excess of a 100 million patient exposures in normal clinical practice as well as extensive observational studies, these limitations are no longer applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

The clinical development programme for duloxetine excluded certain special populations. However, as the product has now been on the market since 2004 and subject to in excess of 100 million exposures in normal clinical practice as well as extensive observational studies, these limitations are no longer applicable.

Module SV - Postauthorisation Experience

SV.1 Postauthorisation Exposure

SV.1.1 Exposure

As of 31 March 2020, the cumulative estimate of worldwide patient exposures to duloxetine is 116 062 000 patients. Cumulative patient-years (PYs) of treatment are estimated to be 43 466 000 PYs.

Table SV.1 provides a global summary of cumulative patient exposure estimates for Cymbalta and Yentreve.

Table SV.1. Exposure Table by Indication Gender, Age Group, Region

Postmarketing Exposure by Age Group and Gender				
Age Group	**Gender**			**Totals[a]**
	Male	**Female**	**Unspecified**	
Cymbalta				
0-11 years	13 000	42 000	--	56 000
12-17 years	421 000	567 000	8000	998 000
18-24 years	1 074 000	2 129 000	55 000	3 259 000
25-64 years	23 775 000	58 003 000	480 000	82 258 000
65-74 years	3 993 000	9 920 000	101 000	14 015 000
75-84 years	2 666 000	6 784 000	52 000	9 503 000
>84 years	553 000	1 395 000	47 000	1 996 000
Unspecified	533 000	1 507 000	399 000	2 440 000
Total[a]	**33 031 000**	**80 352 000**	1 145 000	**114 528 000**
Yentreve				
0-11 years	--	1100	--	1100
12-17 years	--	400	--	400
18-24 years	90	1500	--	1600
25-64 years	37 000	568 000	400	606 000
65-74 years	79 000	400 000	300	479 000
75-84 years	43 000	303 000	200	346 000
>84 years	6000	90 000	--	96 000
Unspecified	90	100	900	1200
Total[a]	**166 000**	**1 365 000**	**2000**	**1 534 000**

Postmarketing Exposure by Country/Region		
Country/Region	**Cumulative Patients**	**Cumulative Patient-Years**
Cymbalta		
Europe	37 439 000	11 997 000
United States	52 131 000	20 108 000
Japan	10 091 000	3 892 000
Other Countries	14 866 000	7 013 000
Worldwide[a]	**114 528 000**	**43 011 000**
Yentreve		
Europe	1 508 000	450 000
United States	not available	not available

Japan	not available	not available
Other Countries	25 000	4000
Worldwide[a]	**1 534 000**	**454 000**

[a] Totals may not sum due to independent rounding.

According to the data in Table SV.1, approximately 0.9% of the total cumulative duloxetine use is in patients under 18 years of age, some of which represents off-label use of duloxetine.

A drug-utilisation study, Study F1J-MC-B038 (B038), conducted in 3 EU countries, showed that duloxetine was one of the less frequently used drugs in paediatric patients in Italy, the UK, and the Netherlands.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

The SNRIs are not known to be drugs of misuse. Eli Lilly and Company (Lilly) regularly reviews its safety database for postmarketing reports of drug abuse/misuse and drug withdrawal. Overall, events related to drug abuse/misuse and drug withdrawal reported with duloxetine use are very rare with no evidence after 15 years marketing of any appreciable intentional and inappropriate use outside the SmPC or misuse for illegal purposes.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable, this is not the initial EU RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Prospective data about potential risks of exposure to duloxetine during pregnancy, previously classified as missing information, is removed from the list of safety concerns.

Duloxetine was first authorised in August 2004 and as of August 2019, it has been authorised in 120 countries, in multiple indications and has a cumulative exposure in excess of 110 million patients globally. In these circumstances, the safety profile of the active chemical substance has been subject to regular scrutiny in multiple global regulatory submissions including Periodic Safety Update Reports/Periodic Benefit-Risk Evaluation Reports (PSUR/PBRERs), RMP update submissions, and responses to regulatory requests. As such, the risk profile is well characterised and without the degree of uncertainty that is associated with a newly authorised medicinal product in its early years on the market.

Duloxetine clinical studies excluded women who were pregnant and required women of childbearing potential to use an effective contraceptive method while in the studies. Although pregnancy occurred in the clinical development programme, there were insufficient data to establish the safety of duloxetine during pregnancy in humans. Studies in animals did not show evidence of embryo lethality, teratogenicity, or fetotoxicity. However, at the time pregnancy was added as a safety concern to the EU RMP, experience in pregnancy was still relatively limited and the target population in the various indications for which duloxetine was authorised were expected to include an appreciable proportion of women of childbearing potential.

Since 2009, a prospective, observational, exposure-registration and follow-up registry (Study F1J-MC-B034, Registry) has been ongoing to monitor pregnancies exposed to duloxetine to determine the risk of birth defects. This study remained in the PV Plan but has been consistently subject to poor recruitment. In order to supplement poor recruitment circumstances of Study B034, 2 observational database studies were implemented and completed:

- Study F1J-MC-B057 (B057), *Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine* (submitted to the EMA within procedure No. EMEA/H/C/WS1527/G which received positive Committee for Medicinal Products for Human Use (CHMP) Opinion on 25 July 2019), and
- Study F1J-MC-B059 (B059), *Observational Study to Assess Fetal Outcomes Following Maternal Exposure to Duloxetine* (submitted to the EMA within procedure No. EMEA/H/C/WS1755 on 31 October 2019 and currently undergoing assessment).

In addition to the observational studies (B034, B057, B059), Lilly has conducted a comprehensive review of scientific literature and pharmacovigilance cases from the Lilly safety database over the last 15 years that the drug has been in the market, and posits that sufficient data

has been collected and evaluated among patients who were exposed to duloxetine during pregnancy. It was reassuring that duloxetine was not associated with overall major malformations.

At this stage in the duloxetine life cycle, it is unlikely that any further study in pregnancy will provide more meaningful information than has already been gleaned from the data sources described above. Therefore, "Prospective data about potential risks of exposure to duloxetine during Pregnancy" has been removed as missing information from the EU RMP.

Overall, the benefit-risk profile for duloxetine continues to be favourable, with the established risks appropriately managed for many years with routine pharmacovigilance and risk management activities. Individual benefit-risk should be performed before exposing women to duloxetine during pregnancy. Duloxetine is indicated for medical conditions with significant morbidity and mortality such as depression, where discontinuing treatment can have severe outcomes for the mother or foetus.

The current product information language recommending that duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus is appropriate and warrants no update based on the results of the Studies B034, B057, and B059.

The use of duloxetine in pregnancy will continue to be monitored in established routine surveillance procedures, and any new findings will be discussed in future PSUR/PBRERs.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Suicidality

Potential mechanisms:

There are no plausible biological mechanisms causally linking suicidality to duloxetine use.

Evidence source(s) and strength of evidence:

Suicidality has been considered a class effect across different antidepressant medicines for many years. Except for young adults and paediatric patients, the evidence linking duloxetine with suicidality is weak, with multiple evidence sources indicating that patients taking duloxetine are not at higher risk for suicidality when compared with placebo-treated patients. These data sources include meta-analyses conducted by Lilly and the US Food and Drug Administration (FDA) regulatory agency, as well as data from observational studies.

The incidence estimates of suicidality in duloxetine-treated patients vary depending on data source and patient characteristics, but overall in postmarketing reporting (even taking into recognised limitations of spontaneous data sources), the reporting rate of suicidality remains very low. Although the results of the different meta-analyses conducted with duloxetine differ, with

one analysis indicating a higher statistical risk than another, the overall trend across the class appears to be in children and in patients younger than 25 years old with psychiatric disorders.

Characterisation of the risk:

Adults

Frequency

- Incidence: 12.85 per 1000 PYs
- Relative Risk: 1.50
- 95% CIs: 0.85-2.66 per 1000 PYs

Data Source: Adult Clinical Trial Data (All Adult Placebo-Controlled Studies), cut-off date: 21 February 2017.

Outcomes

- Fatal: 0 (0.00%)
- Recovered: 25 (0.18%)
- Not recovered: 8 (0.06%)
- Unknown: 1 (0.01%)

Data Source: Adult Clinical Trial Data (All Adult Placebo-Controlled Studies), cut-off date: 21 February 2017.

Children and Adolescents

Frequency

- Incidence: 114.24 per 1000 PYs
- Relative Risk: 1.09
- The 95% CIs: 0.46-2.59 per 1000 PYs

Data Source: Paediatric Clinical Trial Data (Placebo-Controlled Studies), cut-off date: 06 February 2018.

Outcomes

- Fatal: 0 (0.00%)
- Recovered: 10 (1.76%)
- Not recovered: 2 (0.35%)
- Unknown: 0 (0.00%)

Data Source: Paediatric Clinical Trial Data (Placebo-Controlled Studies), cut-off date: 06 February 2018.

Risk factors and risk groups:

Lilly's meta-analyses of placebo-controlled studies with duloxetine suggest that there is a potential but not statistically significantly increased risk of suicidal thinking and behaviour in young adults (aged 18 to 24 years) with duloxetine treatment.

Reversibility

Suicidal and self-injurious behaviour adverse events (AEs) are known to be reversible upon discontinuation of duloxetine. Reversibility would be influenced by any comorbid medical conditions that would predispose the patient to suicidality.

Preventability:

While this risk is not necessarily preventable, the SmPC recommends that close supervision of high-risk patients should accompany drug therapy. An increased risk of suicidal behaviour early after initiating treatment with any antidepressant is a well- known phenomenon to prescribing psychiatrists and has been included in the warnings and precautions section of the SmPC for many years.

Impact on the risk-benefit balance of the product:

Suicidal ideation/behaviour is considered a key risk that contributes most importantly to the overall benefit risk evaluation for the purposes of the PSUR/PBRER. For the purposes of prospective risk management, however, it may no longer fulfil the current definitions and principles of an important risk under prevailing GVP Module V (Rev 2). The risk is well characterised, has not given rise to any new safety signals for many years and has no ostensible impact on benefit risk. The safety profiles for suicidal ideation/behaviour have remained consistent over many years of postmarketing experience and exposure in over 110 million patients with a very rare spontaneous reporting rate (0.0067%). Suicidal ideation/behaviour AEs are known to be reversible upon discontinuation of duloxetine and can be mitigated through appropriate prescribing and monitoring of patients. Duloxetine labelling appropriately includes recommendations to manage this key risk, stating that patients taking duloxetine should be observed for emergence of suicidal thoughts or suicidal behaviours.

Public health impact:

The public health impact of suicidality is considered extremely low, as even after extensive exposure, serious outcomes are very rare. Duloxetine is indicated for a clearly defined subset of the adult population and its use in children and adolescents below the age of 18 is not recommended.

SVII.3.2 Presentation of the Missing Information

Not applicable, there is no missing information for duloxetine.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Suicidality
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including postauthorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for suicidality:

In addition to routine PV activities, specific follow-up forms are used to collect additional scientific/medical data to facilitate evaluation of cases. The follow-up forms listed below relate to listed safety concerns. The information collection will continue as a routine PV activity, despite the removal of most of the safety concerns from the EU RMP, as this will facilitate monitoring in the PSUR/PBRER.

These forms are

- Cardiac arrest (sudden cardiac death), myocardial infarction
- Cardiac failure
- Cerebrovascular accident
- Congenital anomaly
- Death
- Death by suicide
- Gastrointestinal bleeding
- Hepatitis
- Liver failure
- Liver necrosis
- Pregnancy outcome
- Renal failure
- Suicide attempt/ideation, and
- Toxic epidermal necrolysis (TEN).

The forms are located in Annex 4 (Part VII).

Other forms of routine pharmacovigilance activities for safety concerns:

None.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Abbreviations: EU = European Union; RMP = risk management plan; Q = quarter.

Part IV: Plans for Postauthorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine Risk Minimisation Activities
Suicidality	Routine risk communication: SmPC Sections 4.4, 4.8, and 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for close monitoring and supervision of patients for suicidality are included in section 4.4 of the SmPC. • Recommendation not to use in the treatment of children and adolescents under the age of 18 years is included in section 4.4 of the SmPC Other routine risk minimisation measures beyond the Product Information: • None

Abbreviation: SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Suicidality	Routine risk minimisation measures: SmPC Sections 4.4, 4.8, and 5.1 Section 4.4 advises to monitor and supervise patients for suicidality and not to use in treatment of children and adolescents under the age of 18 years. Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up forms for death, death by suicide, and suicide attempt/ideation Additional pharmacovigilance activities: None

Abbreviation: AE = adverse event; SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Cymbalta (duloxetine)

This is a summary of the RMP for Cymbalta. The RMP details important risks of Cymbalta, how these risks can be minimised, and how more information will be obtained about Cymbalta's risks and uncertainties (missing information).

Cymbalta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cymbalta should be used.

This summary of the RMP for Cymbalta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cymbalta's RMP.

I - The Medicine and What It is Used for

Cymbalta is authorised for MDD, DPNP, and GAD (see SmPC for the full indication). Cymbalta contains duloxetine as the active substance and is given by oral administration.

Further information about the evaluation of Cymbalta's benefits can be found in Cymbalta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000572/human_med_000732.jsp&mid=WC0b01ac058001d124.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cymbalta, together with measures to minimise such risks and the proposed studies for learning more about Cymbalta's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A Cymbalta List of Important Risks and Missing Information

Important risks of Cymbalta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is

sufficient proof of a link with the use of Cymbalta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Suicidality
Important potential risks	None
Missing information	None

II.B Cymbalta Summary of Important Risks

Important identified risk: Suicidality	
Evidence for linking the risk to the medicine	Suicidality has been considered a class effect across different antidepressant medicines for many years. With the exception of young adults and paediatric patients, the evidence linking duloxetine with suicidality is weak, with multiple evidence sources indicating that patients taking duloxetine are not at higher risk for suicidality when compared with placebo-treated patients. These data sources include meta-analyses conducted by Lilly and the US Food and Drug Administration (FDA) regulatory agency, as well as data from observational studies. The incidence estimates of suicidality in duloxetine-treated patients vary depending on data source and patient characteristics, but overall in postmarketing reporting (even taking into account recognised limitations of spontaneous data sources), the reporting rate of suicidality is very low. Although the results of the different meta-analyses conducted with duloxetine differ, with 1 analysis indicating a higher statistical risk than another, the overall trend across the class appears to be in children and in patients younger than 25 years old with psychiatric disorders.
Risk factors and risk groups	Lilly's meta-analyses of placebo-controlled studies with duloxetine suggest that there is a potential but not statistically significantly increased risk of suicidal thinking and behaviour in young adults (aged 18 to 24 years) with duloxetine treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.8, and 5.1 Section 4.4 advises to monitor and supervise patients for suicidality and not to use in treatment of children and adolescents under the age of 18 years Additional risk minimisation measures: No risk minimisation measures

II.C Cymbalta Postauthorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Cymbalta.

II.C.2 Other Studies in Postauthorisation Development Plan

There are no studies required for Cymbalta.

Summary of Risk Management Plan for Yentreve (duloxetine)

This is a summary of the RMP for Yentreve. The RMP details important risks of Yentreve, how these risks can be minimised, and how more information will be obtained about Yentreve's risks and uncertainties (missing information).

Yentreve's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Yentreve should be used.

This summary of the RMP for Yentreve should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current concerns will be included in updates of Yentreve's RMP.

I - The Medicine and What It Is Used for

Yentreve is authorised for SUI (see the SmPC for the full indication). Yentreve contains duloxetine as the active substance and is given by oral administration.

Further information about the evaluation of Yentreve's benefits can be found in Yentreve's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000545/human_med_001164.jsp&mid=WC0b01ac058001d124.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Yentreve, together with measures to minimise such risks and the proposed studies for learning more about Yentreve's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine PV activities.

II.A Yentreve List of Important Risks and Missing Information

Important risks of Yentreve are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yentreve. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association

has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Suicidality
Important potential risks	None
Missing information	None

II.B Yentreve Summary of Important Risks

Important identified risk: Suicidality	
Evidence for linking the risk to the medicine	Suicidality has been considered a class effect across different antidepressant medicines for many years. With the exception of young adults and paediatric patients, the evidence linking duloxetine with suicidality is weak, with multiple evidence sources indicating that patients taking duloxetine are not at higher risk for suicidality when compared with placebo-treated patients. These data sources include meta-analyses conducted by Lilly and the US Food and Drug Administration (FDA) regulatory agency, as well as data from observational studies. The incidence estimates of suicidality in duloxetine-treated patients vary depending on data source and patient characteristics, but overall in postmarketing reporting (even taking into account recognised limitations of spontaneous data sources), the reporting rate of suicidality is very low. Although the results of the different meta-analyses conducted with duloxetine differ, with 1 analysis indicating a higher statistical risk than another, the overall trend across the class appears to be in children and in patients younger than 25 years old with psychiatric disorders.
Risk factors and risk groups	Lilly's meta-analyses of placebo-controlled studies with duloxetine suggest that there is a potential but not statistically significantly increased risk of suicidal thinking and behaviour in young adults (aged 18 to 24 years) with duloxetine treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 Section 4.4 advises to monitor and supervise patients for suicidality and not to use in treatment of children and adolescents under the age of 18 years Additional risk minimisation measures: No risk minimisation measures

II.C Yentreve Postauthorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Yentreve.

II.C.2 Other Studies in Postauthorisation Development Plan

There are no studies required for Yentreve.

Summary of Risk Management Plan for Duloxetine Lilly (duloxetine)

This is a summary of the RMP for Duloxetine Lilly. The RMP details important risks of Duloxetine Lilly, how these risks can be minimised, and how more information will be obtained about Duloxetine Lilly's risks and uncertainties (missing information).

Duloxetine Lilly's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Duloxetine Lilly should be used.

This summary of the RMP for Duloxetine Lilly should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current concerns will be included in updates of Duloxetine Lilly's RMP.

I - The Medicine and What It is Used for

Duloxetine Lilly is authorised for MDD, DPNP, and GAD (see the SmPC for the full indication). Duloxetine Lilly contains duloxetine as the active substance and it is given by oral administration.

Further information about the evaluation of Duloxetine Lilly's benefits can be found in Duloxetine Lilly's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004000/human_med_001828.jsp&mid=WC0b01ac058001d124.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Duloxetine Lilly, together with measures to minimise such risks and the proposed studies for learning more about Duloxetine Lilly's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine PV activities.

II.A Duloxetine Lilly List of Important Risks and Missing Information

Important risks of Duloxetine Lilly are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Duloxetine Lilly. Potential risks are concerns for

which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Suicidality
Important potential risks	None
Missing information	None

II.B Duloxetine Lilly Summary of Important Risks

Important identified risk: Suicidality	
Evidence for linking the risk to the medicine	Suicidality has been considered a class effect across different antidepressant medicines for many years. With the exception of young adults and paediatric patients, the evidence linking duloxetine with suicidality is weak, with multiple evidence sources indicating that patients taking duloxetine are not at higher risk for suicidality when compared with placebo-treated patients. These data sources include meta-analyses conducted by Lilly and the US Food and Drug Administration (FDA) regulatory agency, as well as data from observational studies. The incidence estimates of suicidality in duloxetine-treated patients vary depending on data source and patient characteristics, but overall in postmarketing reporting (even taking into account recognised limitations of spontaneous data sources), the reporting rate of suicidality is very low. Although the results of the different meta-analyses conducted with duloxetine differ, with 1 analysis indicating a higher statistical risk than another, the overall trend across the class appears to be in children and in patients younger than 25 years old with psychiatric disorders.
Risk factors and risk groups	Lilly's meta-analyses of placebo-controlled studies with duloxetine suggest that there is a potential but not statistically significantly increased risk of suicidal thinking and behaviour in young adults (aged 18 to 24 years) with duloxetine treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.8, and 5.1 Section 4.4 advises to monitor and supervise patients for suicidality and not to use in treatment of children and adolescents under the age of 18 years Additional risk minimisation measures: No risk minimisation measures

II.C Duloxetine Lilly Postauthorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Duloxetine Lilly.

II.C.2 Other Studies in Postauthorisation Development Plan

There are no studies required for Duloxetine Lilly.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-Up forms

Specific Adverse Event Follow-Up Form	Event(s) Associated with the Form
Form #1	Cardiac arrest (sudden cardiac death), myocardial infarction
Form #2	Cardiac failure
Form #3	Cerebrovascular accident
Form #4	Death by suicide
Form #5	Death
Form #6	Gastrointestinal bleeding
Form #7	Renal failure
Form #8	Suicide attempt/ideation
Form #9	Toxic epidermal necrolysis (TEN)
Form #10	Liver necrosis
Form #11	Hepatitis
Form #12	Congenital anomaly[a]
Form #13	Pregnancy outcome[a]
Form #14	Liver failure

[a] These forms would be modified to add additional questions depending on the foetal/maternal outcome reported.

Form #1 Cardiac arrest (sudden cardiac death), myocardial infarction

Spontaneous Follow-up Form

Reported Events: Cardiac Arrest/Sudden Cardiac Death/Myocardial Infarction

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cardiac Disorders

Primary Diagnosis for the Reported Event(s)

☐ Chest Pain/Angina ☐ Myocardial Infarction ☐ Arrhythmia ☐ Other - please describe:

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Heart rate: _____ ☐ Blood pressure: _____
☐ Palpitations ☐ Shortness of breath
☐ Syncope ☐ Chest pain (please specify): _____
☐ Cardiac exam: _____
☐ Pulmonary exam: _____
☐ Other (please specify): _____

Relevant Medical History (please specify if needed)

☐ Atrial Arrhythmia
☐ Conduction Disorders
☐ Cardiovascular Disease
☐ Cardiovascular Infection
☐ Pulmonary Disease
☐ Metabolic Disorders
☐ Pericarditis
☐ Poor Compliance with BP/Cardiac Meds
☐ Ventricular Arrhythmia
☐ Congenital Heart Abnormalities
☐ Hypertension
☐ Cardiac Surgeries
☐ Pulmonary Embolism
☐ Psychiatric/Emotional Disorders
☐ Syncope
☐ Dizziness
☐ Substance Abuse

☐ Family history of cardiac disease, congenital QT prolongation, premature cardiac death
☐ Other (please specify):_____

Historic Drugs (please specify)

☐ Antiarrhythmics: _____ ☐ Antihypertensives: _____

☐ Psychiatric medications: _____ ☐ Antibiotics: _____

☐ Others:_____

Concomitant Meds (include prescription, substance, OTC and herbal)

☐ Nitrates/Nitrites ☐ Alpha blocker
☐ ED medication (please specify):_____ ☐ Others:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify): _____				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results
EKG (Q waves)/EKG (QTC Interval)	
Myocardial Scan	
Echocardiogram (ECHO)	
Coronary angiography	
Exercise Stress Test	
QT Interval (milliseconds)	
QTc (Corrected Value)	
How was QT interval measured?	○ Machine ○ Manually ○ Other
QT correction formula	○ Bazett ○ Frederica ○ Other
Other (please specify):	

Treatment

☐ Cardioversion/defibrillation ☐ Treatment not required
☐ Medication (please specify):_____ ☐ Ablation
☐ Other (please specify):

Was this event related to a Lilly drug? ☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #2 Cardiac failure

Spontaneous Follow-up Form

Reported Events: Cardiac Failure

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cardiac Disorders

Primary Diagnosis for the Reported Event(s)

☐ Chest Pain/Angina ☐ Myocardial Infarction ☐ Arrhythmia ☐ Other - please describe:

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Heart rate: _____ ☐ Blood pressure: _____
☐ Palpitations ☐ Shortness of breath
☐ Syncope ☐ Chest pain (please specify): _____
☐ Cardiac exam: _____
☐ Pulmonary exam: _____
☐ Other (please specify): _____

Relevant Medical History (please specify if needed)

☐ Atrial Arrhythmia
☐ Conduction Disorders
☐ Cardiovascular Disease
☐ Cardiovascular Infection
☐ Pulmonary Disease
☐ Metabolic Disorders
☐ Pericarditis
☐ Poor Compliance with BP/Cardiac Meds
☐ Ventricular Arrhythmia
☐ Congenital Heart Abnormalities
☐ Hypertension
☐ Cardiac Surgeries
☐ Pulmonary Embolism
☐ Psychiatric/Emotional Disorders
☐ Syncope
☐ Dizziness
☐ Substance Abuse

☐ Family history of cardiac disease, congenital QT prolongation, premature cardiac death
☐ Other (please specify):_____

Historic Drugs (please specify)

☐ Antiarrhythmics: _____ ☐ Antihypertensives: _____

☐ Psychiatric medications: _____ ☐ Antibiotics: _____

☐ Others:_____

Concomitant Meds (include prescription, substance, OTC and herbal)

☐ Nitrates/Nitrites ☐ Alpha blocker
☐ ED medication (please specify):_____ ☐ Others:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify): _____				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results
EKG (Q waves)/EKG (QTC Interval)	
Myocardial Scan	
Echocardiogram (ECHO)	
Coronary angiography	
Exercise Stress Test	
QT Interval (milliseconds)	
QTc (Corrected Value)	
How was QT interval measured?	○ Machine ○ Manually ○ Other
QT correction formula	○ Bazett ○ Frederica ○ Other
Other (please specify):	

Treatment

☐ Cardioversion/defibrillation ☐ Treatment not required
☐ Medication (please specify):_____ ☐ Ablation
☐ Other (please specify):

Was this event related to a Lilly drug?
☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #3 Cerebrovascular accident

Spontaneous Follow-up Form

Reported Events: Cerebrovascular Accident

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No
Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Cerebrovascular Accident

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Presenting Signs/Symptoms

Onset Date: End Date:
Impairments:

☐ Paralysis (specify): _____ ☐ Dysarthria ☐ Impaired consciousness
☐ Weakness (specify): _____ ☐ Visual field defect ☐ Seizure
☐ Dysphagia ☐ Aphasia ☐ Other findings:

Severity

☐ No/Mild ☐ Moderate ☐ Severe

Relevant Medical History

☐ Diabetes ☐ Artrial fibrillation ☐ Head trauma

☐ Smoking ☐ Hypertension ☐ Prior stroke
☐ Myocardial infarction ☐ Hyperlipidemia ☐ Other (please specify):

Relevant Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet Count				
Glucose				
INR				
aPTT				
Thrombin Time				
Fibrinogen				
Other:_____				
Other:_____				

Other Tests	Results
CT	
MRI	
Angiography	
EEG	
Other:	

Treatment

☐ Support and organization ☐ Thrombolytic agent ☐ Ablation
☐ Antiplatelet agent ☐ Anticoagulant ☐ Other:

Was this event related to a Lilly drug?
☐ Yes ☐ No ☐ Unknown

Event Outcome
☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #4 Death by suicide

Spontaneous Follow-up Form

Reported Events: Death by Suicide

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb		○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: Cymbalta® (duloxetine)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Death by Suicide

Date of Death: _____	Cause of death/method used to accomplish suicide:
Was an autopsy performed? ○ Yes ○ No Please provide a copy of the death certificate or autopsy report, if available.	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (e.g. family member), please specify: _____ ☐ Listed on autopsy report

Was the patient's intent to:
Kill self: ○ Definite ○ Questionable ○ No intent ○ Do not know
Provoke others: ○ Definite ○ Questionable ○ No intent ○ Do not know

What was the motive or trigger for the suicide?

☐ Death of a loved one
☐ Relationship failure
☐ Alcohol or substance abuse
☐ Trauma
☐ Other:
☐ Job loss
☐ Divorce
☐ History of aggression or violence
☐ Previous suicide attempts
☐ Family history (mental illness or suicide)
☐ History of victim abuse or neglect
☐ Previous psychiatric diagnosis: _____

Did the patient receive any type of rescue treatment/intervention before death? ○ Yes ○ No
If yes, please describe (include lavage/charcoal/pharmacotherapy):

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Relevant Medical History:

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Form #5 Death

Spontaneous Follow-up Form

Reported Events: Death

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Mortality

Date of Death:	**Underlying Cause of Death:**
Was an autopsy performed? ○ Yes ○ No *Please provide a copy of the death certificate or autopsy report, if available.*	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source of (e.g. family member), please specify: _____ ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ○ No ○ Unlikely ○ Likely ○ Yes ○ Unknown	
Please provide a brief explanation:	

Please provide circumstances surrounding the patient's death and include what symptoms were experienced just prior to death (e.g. chest pain, dyspnea, headache, syncope etc.)

Medical History:

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Form #6 Gastrointestinal bleeding

Spontaneous Follow-up Form

Reported Events: Gastrointestinal Bleeding

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Gastrointestinal Bleeding

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

General Questions

1. What was the anatomic site of bleeding: _____
2. What was the cause of bleeding: _____
3. Grade of bleeding: _____

Was there a procedure performed? ○ No ○ Yes (please specify):

Presenting Signs/Symptoms

- ☐ Hematemesis
- ☐ Hematochezia
- ☐ Melena
- ☐ Abdominal pain
- ☐ Vomiting
- ☐ Retching
- ☐ Fever
- ☐ Diarrhea
- ☐ Occult blood (stool, NG)
- ☐ Other: _____

Concurrent/Recent Events

- ☐ NSAID use
- ☐ Excessive alcohol use
- ☐ Renal failure
- ☐ Hepatic failure
- ☐ Gastritis
- ☐ Corticosteroid use
- ☐ Antibiotics
- ☐ Ventilator use
- ☐ Urinary obstruction
- ☐ Sepsis
- ☐ Burns
- ☐ C difficile colitis

☐ Other: ☐ Recent surgery (specify): ☐ Colonoscopy with biopsy

Medical History

☐ Prior GI bleeding (site):_____
☐ Cancer (site):_____
☐ Peptic ulcer disease
☐ GERD
☐ Hiatal hernia
☐ Inflammatory bowel disease
☐ Colonic polyps
☐ Bleeding disorder (specify):_____
☐ Other (specify):_____
☐ Renal impairment
☐ Cirrhosis
☐ Chronic liver disease
☐ Esophageal varices
☐ Portal hypertension
☐ AV malformation
☐ C difficile colitis
☐ Alcohol overuse

Concomitant Meds/Substances (include prescription, OTC and herbal)

☐ NSAIDS:_____
☐ Corticosteroids:_____
☐ Heparin:_____
☐ Other:_____
☐ Antiplatelet agent:_____
☐ Antibiotics:_____
☐ Proton pump inhibitors:_____
☐ Warfarin

Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin Time				
C. diff toxin				
Other:				
Other:				

Other Study	Results
Endoscopy	
Ultrasound	
CT/MRI	
Biopsy	
Other:_____	

Treatment

☐ Intravenous fluids
☐ Other:
☐ RBC transfusion (units):_____

Was this event related to a Lilly drug?
☐ Yes ☐ No ☐ Unknown
Event Outcome
☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #7 Renal failure

Spontaneous Follow-up Form

Reported Events: Renal failure

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Renal Events

Primary Diagnosis:

Grade of Event: _____

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

- ☐ Oliguria
- ☐ Edema
- ☐ Rash
- ☐ Dyspnea
- ☐ Orthostasis
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Mental status change
- ☐ Flank pain
- ☐ Hematuria
- ☐ Difficult urination
- ☐ Other: _____

Concurrent/Recent Events

- ☐ Hypotension
- ☐ Hemorrhagic shock
- ☐ Septic shock
- ☐ Cardiogenic shock
- ☐ Nephrotoxic agents
- ☐ Iodinated contrast
- ☐ Burns
- ☐ Severe dehydration
- ☐ Urinary obstruction
- ☐ Diarrhea
- ☐ Other: _____

Relevant Medical History

- ☐ Diabetes
- ☐ Renal disease:_____
- ☐ Cancer:_____
- ☐ Collagen/vascular disease:_____
- ☐ Congestive heart failure
- ☐ Multiple myeloma
- ☐ Hypertension
- ☐ Nephrolithiasis
- ☐ Prostatic hypertrophy
- ☐ Urinary obstruction
- ☐ Chronic liver disease
- ☐ Other:_____

Concomitant Meds (include prescription, substance, OTC and herbal)

- ☐ NSAIDS
- ☐ Other:_____

Relevant Laboratory Tests	Normal Range for your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Creatinine				
BUN				
Sodium				
Potassium				
CPK				
Hemoglobin				
WBC				
Platelets				
INR				
Urine sodium				
Urine osmolality				
Urine Protein (please indicate method): ☐ Urinalysis ☐ 24 Hour Urine Collection ☐ Other				
Other:_____				

Other Studies	Results
Urinalysis	☐ RBC casts ☐ WBC casts ☐ Other:_____
Renal ultrasound	
Renal CT/MRI	
Renal biopsy	
Other:_____	

Treatment

- ☐ Intravenous fluids
- ☐ RBC transfusion
- ☐ Other:_____
- ☐ Dialysis
- ☐ Corticosteroids

Was this event related to a Lilly drug?

	☐ Yes ☐ No ☐ Unknown
Event Outcome ☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

*Please provide rationale for relatedness assessment:

Form #8 Suicide attempt/ideation

Spontaneous Follow-up Form

Reported Events: Suicide attempt/ideation

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb		○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: Cymbalta® (duloxetine)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Suicide Attempt \ Ideation

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Relevant Medical History:

Circumstances:

☐ Self-inflicted Harm ☐ Suicide Attempt ☐ Suicidal Ideation

Was the patient's intent to:

Kill self? ○ Definite ○ Questionable ○ No intent ○ Do not know

Provoke others? ○ Definite ○ Questionable ○ No intent ○ Do not know

What was the motive or trigger?

☐ Death of a loved one
☐ Relationship failure
☐ Alcohol or substance abuse
☐ Trauma
☐ Job loss
☐ Divorce
☐ History of aggressive or violent behavior
☐ Previous suicide attempts
☐ Family history of mental illness or suicide attempts
☐ History of victim of abuse or neglect
☐ Previous psychiatric diagnosis (please explain):

_____

☐ Other:

Did the patient receive any type of rescue treatment/intervention?
○ Yes ○ No
If yes, please describe (include lavage/charcoal/pharmacotherapy):

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Was this event related to a Lilly drug?
Suicide attempt/ideation D Yes D No D Unknown

Event Outcome
D Recovered D Not Recovered D Recovering D Worsened D Unknown
D Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #9 Toxic epidermal necrolysis (TEN)

Spontaneous Follow-up Form

Reported Events: Toxic Epidermal Necrolysis

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Skin and Subcutaneous Tissue

Primary Diagnosis for the Reported Event(s)

☐ Toxic Epidermal Necrolysis ☐ Stevens-Johnson Syndrome ☐ Erythema Multiforme
☐ Bullous Rash ☐ DRESS ☐ Other: _____

Hospitalization for this event? ○ Yes ○ No

Concomitant Medications/Substances(please include prescription, OTC and herbal)

Clinical Course

Start Date (mm/dd/yyyy): _____ Stop Date (mm/dd/yyyy): _____

Body surface area involved: ○ 10% ○ 10-30% ○ >30%

Have any target lesion been seen? ○ Yes ○ No Comments: _____

Any mucosal involvement (e.g., oral, genital) ○ Yes ○ No Comments: _____

Suggestion of Nikolsky's sign? ○ Yes ○ No Comments: _____

Additional description and treatment provided:

Medical History

☐ Drug, dye, food, preservative, other intolerance/allergies: _____

☐ Antigen sensitivity (specify):_____
☐ Vasculitis:_____
☐ Atopy:_____
☐ Infections:_____
☐ Occupational risks:_____
☐ Skin disease:_____
☐ Anaphylactic reactions:_____
☐ Family history of skin reactions/allergies:_____
☐ Other (specify):_____

Diagnostic Test	Results (include units of measurement)
Skin biopsy	
Drug levels	
Skin tests (specify): _____	
Immunoglobulins	
Autoimmune profile (specify): _____	
Sensitivity test	
Eosinophil count	
ALT	

Was this event related to a Lilly drug?
☐ Yes ☐ No ☐ Unknown

Event Outcome
☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #10 Liver necrosis

Spontaneous Follow-up Form

Reported Events: Liver necrosis

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No
Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Hepatic Disorders

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Fever	☐ Jaundice	☐ Abdominal Pain
☐ Rash	☐ Edema	☐ Ascites
☐ Joint Effusions	☐ Nausea	☐ Palmar Erythema
☐ Urticaria	☐ Confusion	☐ Asterixis
☐ Arthralgias	☐ Other: _____	

Concurrent Events and Disease(s)

☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Other: _____	

Concurrent Disease(s)

☐ HIV	☐ Cor pulmonale	☐ Malignancy
☐ Tuberculosis	☐ Autoimmune disease	☐ Inflammatory bowel disease
☐ Congestive heart failure	☐ Diabetes	☐ Other: _____

Relevant Past Medical History

- ☐ None
- ☐ Hepatitis A
- ☐ Hepatitis B
- ☐ Hepatitis C
- ☐ Gall bladder disease
- ☐ Fatty liver
- ☐ Liver toxin exposure
- ☐ Cirrhosis Child Pugh B or C
- ☐ Alcoholic liver disease
- ☐ Autoimmune hepatitis
- ☐ Hyperbilirubinemia/Jaundice
- ☐ Abnormal liver laboratory results
- ☐ Budd-Chiari syndrome
- ☐ Hepatic encephalopathy
- ☐ Ascites
- ☐ Hepatorenal syndrome
- ☐ Portal Hypertension
- ☐ Other:_____

Concomitant Meds/Substances (include prescription, OTC and herbal):

- ☐ Current Alcohol
- ☐ Past Alcohol
- ☐ Current Tobacco
- ☐ Past Tobacco
- ☐ Current Cocaine/Methamphetamine
- ☐ Past Cocaine/Methamphetamine
- ☐ Other:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				

Serologic Studies (check positive)

- ☐ Anti-nuclear Antibody (ANA)
- ☐ Anti-liver Kidney Microsomal (antiLKM)
- ☐ Anti-actin
- ☐ Anti-smooth Muscle Antibody (ASMA)
- ☐ Cytomegalovirus (CMV) Antibody IgM
- ☐ Ebstein Barr (EBV) Serology
- ☐ Other:_____
- ☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
- ☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
- ☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
- ☐ Hepatitis B Virus Surface Antibody (anti-HBs)
- ☐ Hepatitis B Virus Surface Antigen (HBs Ag)
- ☐ Hepatitis C Virus Antibody (anti-HCV)
- ☐ Hepatitis C Virus RNA (HCV RNA)

Other Study	Results
Liver Biopsy	
Hepatic Ultrasound	
MRI	
CT Scan	

Other: _____

Treatment provided (please describe)

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #11 Hepatitis

Spontaneous Follow-up Form

Reported Events: Hepatitis

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No
Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Hepatic Disorders

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Fever	☐ Jaundice	☐ Abdominal Pain
☐ Rash	☐ Edema	☐ Ascites
☐ Joint Effusions	☐ Nausea	☐ Palmar Erythema
☐ Urticaria	☐ Confusion	☐ Asterixis
☐ Arthralgias	☐ Other: _____	

Concurrent Events and Disease(s)

☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Other: _____	

Concurrent Disease(s)

☐ HIV	☐ Cor pulmonale	☐ Malignancy
☐ Tuberculosis	☐ Autoimmune disease	☐ Inflammatory bowel disease
☐ Congestive heart failure	☐ Diabetes	☐ Other: _____

Relevant Past Medical History

☐ None ☐ Liver toxin exposure ☐ Budd-Chiari syndrome
☐ Hepatitis A ☐ Cirrhosis Child Pugh B or C ☐ Hepatic encephalopathy
☐ Hepatitis B ☐ Alcoholic liver disease ☐ Ascites
☐ Hepatitis C ☐ Autoimmune hepatitis ☐ Hepatorenal syndrome
☐ Gall bladder disease ☐ Hyperbilirubinemia/Jaundice ☐ Portal Hypertension
☐ Fatty liver ☐ Abnormal liver laboratory results ☐ Other:_____

Concomitant Meds/Substances (include prescription, OTC and herbal):

☐ Current Alcohol ☐ Current Tobacco ☐ Current Cocaine/Methamphetamine
☐ Past Alcohol ☐ Past Tobacco ☐ Past Cocaine/Methamphetamine
☐ Other:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				

Serologic Studies (check positive)

☐ Anti-nuclear Antibody (ANA)
☐ Anti-liver Kidney Microsomal (antiLKM)
☐ Anti-actin
☐ Anti-smooth Muscle Antibody (ASMA)
☐ Cytomegalovirus (CMV) Antibody IgM
☐ Ebstein Barr (EBV) Serology
☐ Other:_____
☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
☐ Hepatitis B Virus Surface Antibody (anti-HBs)
☐ Hepatitis B Virus Surface Antigen (HBs Ag)
☐ Hepatitis C Virus Antibody (anti-HCV)
☐ Hepatitis C Virus RNA (HCV RNA)

Other Study	Results
Liver Biopsy	
Hepatic Ultrasound	
MRI	
CT Scan	

Other: _____

Treatment provided (please describe)

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #12 Congenital anomaly

Spontaneous Follow-up Form

Reported Events: Congenital Anomaly

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
◯ F ◯ M ◯ Unknown	◯ Caucasian	◯ Asian	_____	◯ lb		◯ in
	◯ Black	◯ Other		◯ kg		◯ cm

Reported Drug: Cymbalta® (duloxetine)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ◯ No ◯ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ◯ Yes ◯ No

Drug Restarted? ◯ No ◯ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ◯ Yes ◯ No

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	◯ M ◯ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Contraceptive method: _____

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
◯ 0-12 weeks/1st trimester ◯ 13-24 weeks/2nd trimester ◯ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes
Define complications:

Treatment:

Continuing: ○ No ○ Yes
Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Pregnancy/Fetal Outcome

○ Live birth/full term
○ Premature birth (less than 37 weeks)
○ Spontaneous/missed abortion
○ Fetal death in utero/stillbirth
○ Live birth with neonatal death
○ Post natal death

Were congenital or chromosomal abnormalities detected? ○ No ○ Yes
Please define:

Neonatal/Infant Data

Infant name or initials:_____EDC (Due Date):_____Date of Delivery:_____
Gestational age:_____Gender: ○ Undetermined/unknown ○ Male ○ Female
Apgar scores: at 1 minute_____at 5 minutes _____
Weight:_____○ grams ○ pounds Length:_____○ cm ○ inches
Infant's overall healthy status?

Infant Adverse Events/Complications

Did the infant experience any problems while breast feeding? ○ No ○ Yes
Please describe:

Treatment:

Continuing: ○ No ○ Yes

Infant's overall health status: _____

Additional Contact Information

Medical professional responsible for monitoring patient's pregnancy:

Medical professional responsible for monitoring the infant:

Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Was this event related to a Lilly drug?

Congenital Anomaly D Yes D No D Unknown

Event Outcome

D Recovered D Not Recovered D Recovering D Worsened D Unknown

D Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #13 Pregnancy outcome

Spontaneous Follow-up Form

Reported Events: Pregnancy Outcome

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb		○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: Cymbalta® (duloxetine)

Lot/Control Number (if available): _____ **Indication:** _____

Dose: _____ **Frequency:** _____ **Formulation:** _____

Start Date: _____ **Dose when event occurred:** _____ **Route:** _____

Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No

Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials: _____ Date of Birth or Age: _____

Due Date: _____ Last menstrual period: _____

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	○ M ○ F				

Maternal medical history/risk factors (e.g., hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, etc.)

Contraceptive method: _____

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
○ 0-12 weeks/1st trimester ○ 13-24 weeks/2nd trimester ○ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance(please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ○ No ○ Yes
Define complications:

Treatment:

Continuing: ○ No ○ Yes
Maternal Testing Performed (i.e., amniocentesis, ultrasound, etc.)

Pregnancy/Fetal Outcome

○ Live birth/full term
○ Premature birth (less than 37 weeks)
○ Spontaneous/missed abortion
○ Fetal death in utero/stillbirth
○ Live birth with neonatal death
○ Post natal death

Were congenital or chromosomal abnormalities detected? ○ No ○ Yes
Please define:

Neonatal/Infant Data

Infant name or initials:_____EDC (Due Date):_____Date of Delivery:_____
Gestational age:_____Gender: ○ Undetermined/unknown ○ Male ○ Female
Apgar scores: at 1 minute_____at 5 minutes _____
Weight:_____○ grams ○ pounds Length:_____○ cm ○ inches
Infant's overall healthy status?

Infant Adverse Events/Complications

Did the infant experience any problems while breast feeding? ○ No ○ Yes
Please describe:

Treatment:

Continuing: ○ No ○ Yes

Infant's overall health status: _____

Additional Contact Information

Medical professional responsible for monitoring patient's pregnancy:

Medical professional responsible for monitoring the infant:

Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Was this event related to a Lilly drug?

Pregnancy Outcome D Yes D No D Unknown

Event Outcome

D Recovered D Not Recovered D Recovering D Worsened D Unknown

D Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Form #14 Liver failure

Spontaneous Follow-up Form

Reported Events: Liver failure

Date: _____ **Lilly Case #:** _____
Information Provided By: _____ **Signature / Initials:** _____ **Fax:** _____

Patient Name or Initials: _____ **Patient Birth Date or Age:** _____

Gender:	**Race:**		**Weight:**		**Height:**	
○ F ○ M ○ Unknown	○ Caucasian	○ Asian	_____	○ lb	_____	○ in
	○ Black	○ Other		○ kg		○ cm

Reported Drug: _____
Lot/Control Number (if available): _____ **Indication:** _____
Dose: _____ **Frequency:** _____ **Formulation:** _____
Start Date: _____ **Dose when event occurred:** _____ **Route:** _____
Drug D/C? ○ No ○ Yes **Date D/C:** _____ **If Discontinued, did the event resolve?** ○ Yes ○ No
Drug Restarted? ○ No ○ Yes **Date Restarted:** _____ **If Restarted, did the event reoccur?** ○ Yes ○ No

Hepatic Disorders

Primary diagnosis for the reported event(s):

Hospitalization for this event? ○ Yes ○ No

Presenting Signs/Symptoms

☐ Fever	☐ Jaundice	☐ Abdominal Pain
☐ Rash	☐ Edema	☐ Ascites
☐ Joint Effusions	☐ Nausea	☐ Palmar Erythema
☐ Urticaria	☐ Confusion	☐ Asterixis
☐ Arthralgias	☐ Other: _____	

Concurrent Events and Disease(s)

☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Other: _____	

Concurrent Disease(s)

☐ HIV	☐ Cor pulmonale	☐ Malignancy
☐ Tuberculosis	☐ Autoimmune disease	☐ Inflammatory bowel disease
☐ Congestive heart failure	☐ Diabetes	☐ Other: _____

Relevant Past Medical History

- ☐ None
- ☐ Hepatitis A
- ☐ Hepatitis B
- ☐ Hepatitis C
- ☐ Gall bladder disease
- ☐ Fatty liver
- ☐ Liver toxin exposure
- ☐ Cirrhosis Child Pugh B or C
- ☐ Alcoholic liver disease
- ☐ Autoimmune hepatitis
- ☐ Hyperbilirubinemia/Jaundice
- ☐ Abnormal liver laboratory results
- ☐ Budd-Chiari syndrome
- ☐ Hepatic encephalopathy
- ☐ Ascites
- ☐ Hepatorenal syndrome
- ☐ Portal Hypertension
- ☐ Other:_____

Concomitant Meds/Substances (include prescription, OTC and herbal):

- ☐ Current Alcohol
- ☐ Past Alcohol
- ☐ Current Tobacco
- ☐ Past Tobacco
- ☐ Current Cocaine/Methamphetamine
- ☐ Past Cocaine/Methamphetamine
- ☐ Other:_____

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				

Serologic Studies (check positive)

- ☐ Anti-nuclear Antibody (ANA)
- ☐ Anti-liver Kidney Microsomal (antiLKM)
- ☐ Anti-actin
- ☐ Anti-smooth Muscle Antibody (ASMA)
- ☐ Cytomegalovirus (CMV) Antibody IgM
- ☐ Ebstein Barr (EBV) Serology
- ☐ Other:_____
- ☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
- ☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
- ☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
- ☐ Hepatitis B Virus Surface Antibody (anti-HBs)
- ☐ Hepatitis B Virus Surface Antigen (HBs Ag)
- ☐ Hepatitis C Virus Antibody (anti-HCV)
- ☐ Hepatitis C Virus RNA (HCV RNA)

Other Study	Results
Liver Biopsy	
Hepatic Ultrasound	
MRI	
CT Scan	

Other: _____

Treatment provided (please describe)

Was this event related to a Lilly drug?

☐ Yes ☐ No ☐ Unknown

Event Outcome

☐ Recovered ☐ Not Recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

*Please provide rationale for relatedness assessment:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.