A methodological study using dispensing data as a source for safety monitoring of marketed drugs

Master's thesis by

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Abstract

Background: Today it is well recognized that it is not possible to fully determine the safety of a medicinal product prior to marketing authorization. Even though there are strict requirements that need to be met before a drug can be introduced to the market, new safety risks may come to light at any time point throughout the life of a drug. Therefore, there is a need for safety monitoring of marketed drugs. In Denmark the Danish Health and Medicines Authority (DHMA) monitors the safety of marketed drugs by means of different methods and sources. Not all of these are equally widely used by the DHMA and they would like to expand the use of some of the sources in order to enhance the safety monitoring of drugs. One of these sources is the Register of Medicinal Product Statistics (RMPS). The RMPS is a register which is owned and managed by the DHMA. The register is the only register of its kind, containing data on redeemed prescriptions of an entire population over many years and thereby holds unique opportunities in regard to investigating how and to what extent a drug is used in Denmark. It is possible that such an investigation can contribute to safety monitoring.

Aim: The aim of this study was to investigate whether and how methods for investigating the utilization of a drug by using dispensing data available in the RMPS can contribute to safety monitoring at the DHMA in the future. To investigate this, the utilization of the antidepressants Cymbalta and Xeristar was investigated as an example.

Materials and methods: This was a register-based retrospective study. The study population consisted of Danish residents who redeemed at least one prescription of Cymbalta/Xeristar from1st of January 2005 to 31st of December 2010. Several aspects of the drug utilization were investigated. These were: size and composition of the user population in regard to age and gender distribution, switch between drugs, average amount of redeemed drug in Defined Daily Doses (DDDs), and concomitant use with contraindicated drugs. By comparing the results to the recommended use of the drugs, the extent of off-label use was investigated.

Results: In this study it was found that users of Cymbalta/Xeristar in Denmark were of both genders and in all age groups. Furthermore, it was found that the average amount of redeemed drug in DDDs per user increased over the study period. It was also detected that some users switched to another antidepressant and that some were in concomitant treatment with contraindicated drugs.

Conclusion: By means of the applied methods it was possible to investigate the utilization of Cymbalta/Xeristar and based on this detect alarming tendencies in the drug utilization which constituted potential safety issues for the users. It was discussed that an investigation using the methods demonstrated in this study could also be performed for other drugs when adjusted to the drug in question. In regard to this, it should be considered that the applied methods have both strengths and limitations and are more applicable for some drugs than others. Overall it was suggested that the methods applied in this study using dispensing data available in the RMPS offer an additional approach with widespread applicability for safety monitoring at the DHMA.

Preface

This Master´s thesis was written by Anja Nygaard Johansen and Annette Aalykke Stenzhorn, 3rd-4th semester of the Master´s degree programme in Medicine with Industrial Specialization, Department of Health Science and Technology, Aalborg University. The thesis was devised from September 1st 2011 to June 1st 2012 at the department of Pharmacovigilance and Medical Devices at the Danish Health and Medicines Authority (the former Danish Medicines Agency). The authors contributed equally to the thesis.

The aim of the thesis was to investigate whether and how methods for investigating the utilization of a drug by means of dispensing data from the Register of Medicinal Products Statistics can contribute to safety monitoring. To investigate this, the methods for the investigation were demonstrated with an example. The chosen example was antidepressants with the active ingredient duloxetine (Cymbalta and Xeristar). Aspects which were investigated were size and composition of user population, patterns of drug use and off-label use.

The thesis is organized in chapters with a general introduction to topics relevant to the purpose of the thesis in the first chapter. Subsequently the aim of the project is presented and the materials and methods are described. The results are presented and afterwards discussed. Lastly, a conclusion is made. The discussion and conclusion reflect the views of the authors.

References and appertaining reference list is structured based on the Vancouver system. Some of the background knowledge of the work of the Danish Health and Medicines Authority was obtained from employees at the Danish Health and Medicines Authority and therefore have no references.

In the thesis abbreviations are used for some words. The words for which abbreviations are assigned are spelled out the first time they are used and the abbreviations are presented in parentheses.

We would like to thank our internal supervisor, Parisa Gazerani, Associate Professor, Department of Health Science and Technology, Aalborg University and our external supervisor, Mary Rosenzweig, Academic Employee, Pharmacovigilance and Medical Devices, Danish Health and Medicines Authority, for their support and guidance throughout the work with the thesis. We would also like to thank Steffen Thirstrup, Director of Licensing Division, Danish Health and Medicines Authority, for sharing his medical expertise in regard to specific matters of the thesis. Furthermore, we would like to thank the employees at the Danish Health and Medicines Authorities in general for support throughout the work with the thesis.

Table of contents

1 Introduction

Today it is well recognized that it is not possible to fully determine the safety of a medicinal product prior to marketing authorization.[1] Even though there are strict requirements that need to be met before a drug can be introduced to the market, new safety risks may come to light at any time point throughout the life cycle of a drug.[2,3] This is due to the fact that the conditions under which the drugs are tested in clinical trials before marketing do not reflect the conditions under which the drugs are used in real life.[3,4] First of all, the population of participants in clinical trials is very restricted, often excluding subpopulations such as children, elderly, patients with comorbidities, and patients taking other drugs than the one being tested.[5] Secondly, the number of participants exposed to the drug through the clinical trials ranges from hundreds to a few thousand patients. Once marketed, the drug will become available to a larger and more heterogeneous group of patients, than the one included in the clinical trials.[4,6] Also, the relatively short duration of clinical trials is not sufficient to detect possible long-term consequences of the drug being tested.[6] Additionally, participants in clinical trials will be observed closely through medical visits and more tests are also usually performed than under real life circumstances. This intensive monitoring of patients is typically not performed in real life.[4] Other aspects in continuation of this, which pre-marketing studies cannot predict, is how the drug will be used in real life in regard to prescribing patterns by physicians and patient compliance. In clinical trials the prescribing patterns are well-specified, whereas the prescribing patterns in real life are often more diverse.[2] The diverse prescribing patterns are e.g. caused by patients switching drugs due to side effects.[4] Another cause is that after marketing, drugs are often prescribed for indications, doses etc. outside the recommendations of the Summary of Product Characteristics (SPC), i.e. off-label use.[7] As a result of the limitations in clinical trials mentioned above, it is important to monitor and evaluate the effectiveness and safety of drugs after they have been marketed.[4]

Effectiveness and safety of drugs are monitored through different post-marketing activities.[4] Such activities are not subject to many of the limitations, which are associated with the pre-marketing clinical trials. Through post-marketing activities the effect of a drug in the subpopulations, which are often excluded in the pre-marketing clinical trials, can be established as the drug is available to and possibly used by these subpopulations. Additionally, this enables investigations of whether and how the effect of the drug is altered due to factors such as comorbidities and concomitant treatment of other drugs. Since the number of patients exposed to the drug once it is marketed is much larger than the number of patients included in pre-marketing clinical trials, detection of rare adverse drug reactions (ADRs) is possible. Furthermore, the estimation of the effect of the drug is more accurate than in pre-marketing studies. As post-marketing activities, on the contrary to pre-marketing clinical trials, are not necessarily subject to a time constraint, it is possible to study potential long-term effects of a drug. Through post-marketing activities it is also possible to investigate the prescribing patterns in real life.[8] The differences between conditions in pre-marketing and post-marketing phases are summarized in figure 1.

1.1 Pharmacovigilance

The post-marketing activities related to safety monitoring are collected under the term pharmacovigilance.[4] The World Health Organization (WHO) defines pharmacovigilance as:

> *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems."*[9]

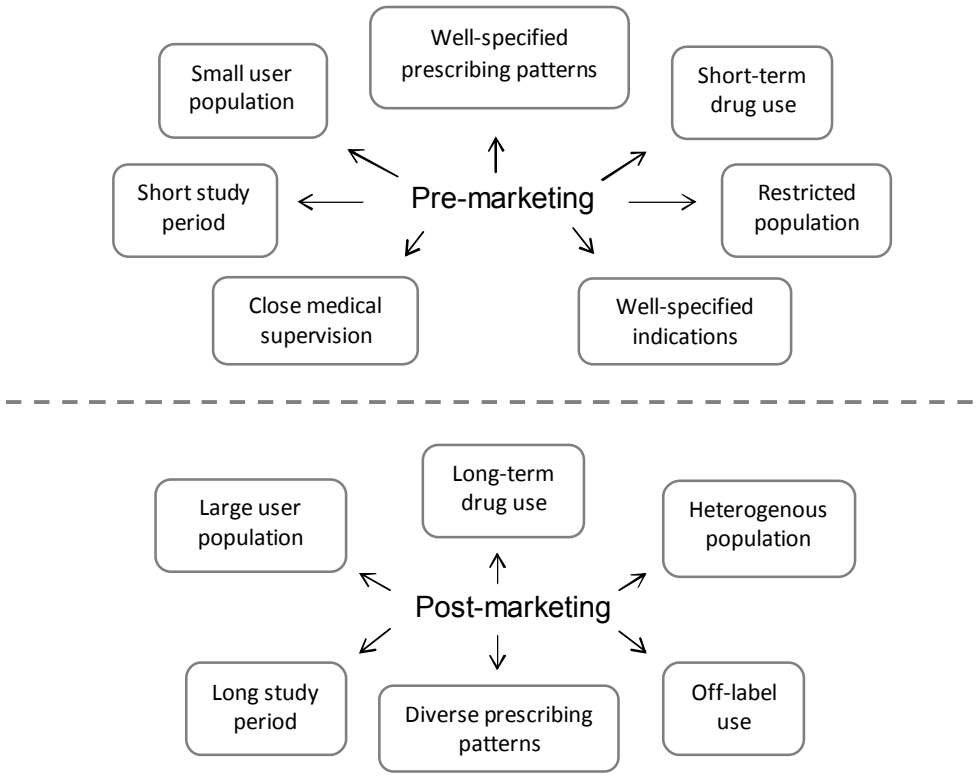

Figure 1. Differences between conditions in the pre-marketing and post-marketing phases. The figure is devised by the authors on the basis of a figure devised by Glasser and colleagues.[4]

The aims of pharmacovigilance are to improve safety of drugs, contribute to obtaining further knowledge and supporting existing knowledge on benefits and harms of drugs, and promote spreading of knowledge in the field of pharmacovigilance. The science and performance of pharmacovigilance first emerged in the wake of the thalidomide disaster, which took place in 1961-1962.[9,10] Thalidomide was claimed to be a safe drug used e.g. as an anti-emetic and therefore many pregnant women used it in early pregnancy. However, it turned out that the drug was not as safe as claimed, as it caused birth defects in around 10,000 children.[10] The thalidomide affair made it clear that systems addressing safety issues of marketed drugs were needed. As a result systems for monitoring safety of drugs were established in several countries. The function of these systems was to enhance the safety of drugs and avoid cases like the thalidomide disaster, and contribute with knowledge for the work of regulatory agencies.[9] Since then, many centers and systems for monitoring drug safety have been established. This include national and international pharmacovigilance centers, but also within the pharmaceutical industry systems for monitoring safety of drugs have been and are still being established and expanded.[1,9,11]

1.1.1 Current methods in pharmacovigilance

The methods used in pharmacovigilance to monitor the safety of drugs are in general the same for regulatory authorities and pharmaceutical companies.[11] Overall they aim to detect and investigate signals of potential safety issues of a drug. A signal is an alert that there might be a causal relationship between a drug and a hazard not previously recognized or a known hazard which is expressed more frequent or is of a more serious character than expected.[3] The signals detected can then be followed up and based on this it

is decided whether action should be taken to enhance safety of the drug being investigated. The actions which can be taken can be adding contraindications or changing recommendations on doses in the SPC. It is also possible that a drug can be withdrawn from the market as it might be found that the benefits do not overweigh the harms anymore.[3]

The methods used in pharmacovigilance are either hypothesis-generating or hypothesis-testing. Hypothesis-generating methods aim to detect signals of potential safety issues, whereas hypothesis-testing methods aim to test whether the generated hypotheses are true or not.[10]

The first system developed in pharmacovigilance included collection of spontaneous reports on ADRs with the purpose of detecting ADRs as soon as possible.[1] This is still the primary method used in safety monitoring of marketed drugs today.[6,12] Collecting and analyzing spontaneous reports of ADRs are primarily used for detecting signals and generating hypotheses but can also be used for testing hypotheses.[10,11] The approach constitutes a passive surveillance system which means that the reports are not actively collected.[12,13] The spontaneous reports are collected and analyzed by e.g. regulatory authorities to monitor safety of marketed drugs.[6] The analyses are typically performed by means of data mining, which consist of automated systems able to detect signals.[9,14] There are both advantages and disadvantages in using spontaneous reports in safety monitoring. One advantage is that it is a low-cost method which enables authorities and the pharmaceutical industry to monitor drugs throughout their life cycle. Furthermore, the method is indispensable in regard to signal detection. However, underreporting is common and spontaneous reports cannot stand alone in determining how frequent an ADR is.[6,9]

Besides from collecting spontaneous reports, other methods and sources are being used to generate hypotheses in safety monitoring.[10] These sources include different patient registers and databases of medical records.[5] Contrary to the spontaneous reporting systems, these constitute active surveillance systems, which consist of actively, and without interfering with prescription of drugs, collecting information on populations of users in treatment with marketed drugs.[13] Registers and databases are considered to gain increasing importance in pharmacovigilance as they offer quick and relatively inexpensive ways to generate hypotheses and address questions about drugs which requires large sample sizes to be investigated.[5] Besides from being used for generating hypotheses the registers and databases can also often be used to test hypotheses.[10,13] It varies from country to country which types of registers and databases are available and how they are designed. Some databases contain data on both drug exposure and outcome, whereas others hold the information in separate databases. In cases where the data is hold in different databases it is possible to link the data by means of an identification code, if needed. The registers and databases both have advantages and disadvantages. An advantage is that it, as mentioned, is an inexpensive source of information and furthermore it is very efficient. However, the data kept in the databases are often collected for other purposes and therefore they may lack information relevant to some studies. Moreover, there is a risk of bias as there is no randomization.[13]

Performing clinical trials is also a tool used for active surveillance in pharmacovigilance. [13]They are performed to test hypotheses.[10] The advantage of clinical trials performed after marketing for pharmacovigilance purposes is that the risk of bias, which is present in observational studies, is removed. However, due to the fact that most serious ADRs are uncommon, the clinical trials performed after marketing require a larger group of patients compared to clinical trials performed before licensing and furthermore they are also typically performed over a longer period.[10,13]

1.1.2 Development within the field of pharmacovigilance

The field of pharmacovigilance has evolved a lot since it emerged in the 1960's and it is still evolving.[6] Not only are new sources being used in pharmacovigilance, but it has also been recognized in the last decades that drug safety includes more than monitoring ADRs. E.g. aspects as irrational drug use, and polypharmacy and interactions have not received as great attention in drug safety monitoring as ADRs, but these aspects are also important to drug safety and should therefore be addressed.[9] Consequently, systems are being reformed and new methods are continuously developed with the purpose of including more aspects in drug safety monitoring.[6,9]

Furthermore, a development which is happening within pharmacovigilance is that the cooperation between the different parties working with pharmacovigilance is continuously increasing and they share information on an international level.[11] It is recognized that this international cooperation is important in order for pharmacovigilance to be a success. Therefore, there is a lot of focus on enhancing and improving the cooperation. International centers, such as the WHO Uppsala Monitoring Centre, are contributing to this by promoting communication between countries.[9]

Initiatives are also made on a legal level to enhance pharmacovigilance. An initiative which has recently been made within the EU to optimize pharmacovigilance and strengthen the cooperation and communication throughout the EU is a legislation from 2010, which will become valid in July 2012.The goal is that patient safety and public health in general will be enhanced through optimization of prevention, detection, and assessment of ADRs.[15] To do this, the legislation includes changes in evaluation of drug associated risks and harmonization in actions taken on a regulatory plan in regard to drug safety as well as increased cooperation throughout the EU and increased transparency.[16]

The above mentioned is just some of the initiatives and developments which are currently taking place within the field of pharmacovigilance. It illustrates that it is a field subject to continuous changes and improvements, all performed with the purpose of enhancing drug safety monitoring.

1.2 Pharmacovigilance at the Danish Health and Medicines Authority

The safety of drugs available on the Danish market is monitored by the Danish Health and Medicines Authority (DHMA), which is the authority in Denmark responsible for managing the regulation of drugs on the Danish market.[17-19] In summary, the work with monitoring the safety of drugs consist of obtaining information on the drugs available on the Danish market from different sources and based on this detect potential safety issues which may need to be investigated further. The potential safety issues which are detected can be followed up in signal analyses established and performed by the DHMA to investigate the specific matter. The signal analyses can also be performed in cooperation with the National Institute for Health Data and Disease Control. Besides from following up safety signals in signal analyses, certain safety issues are brought up and evaluated on an international level. Based on the findings on drug safety it is then decided whether action should be taken. These actions can include, as mentioned previously, changing the SPC or withdrawing the marketing authorization.

The DHMA currently have different approaches and sources, which they use in their work with monitoring safety of marketed drugs. The main source used in their work with safety monitoring is spontaneous reports on ADRs. These are reported to the DHMA from patients, health care professionals, and pharmaceutical companies.[19,20] When submitted to the DHMA, the spontaneous reports on ADRs are registered in a database and the serious ADRs are reviewed on a daily basis.[19] When ADRs of a certain severity is

reported, it is evaluated whether there might be a causal relationship between the drug and the reported ADR.[19] One of the recent initiatives taken by the DHMA to improve the work with the spontaneous reports on ADRs is introducing the data mining tool Oracle Health Sciences Empirica Signal. This constitutes a tool which is able to detect whether there are safety signals, undesirable patterns, and/or emerging trends in data on spontaneous reports of ADRs. The system holds many features which improve the work with the spontaneous reports. Some of the features are that the system quantifies safety signals and prioritize most important risks.[21]

There are also other sources which can generate safety signals and prepare the ground for signal analyses. E.g. different cases brought in the media can lead to attention to specific issues which need to be investigated. There can also be findings in international studies or signals from other authorities, e.g. the Food and Drug Administration (FDA) or WHO, which can prepare the ground for signal analyses at the DHMA.

Another source used in the work is Periodic Safety Update Reports (PSURs) which the market authorization holder is obligated to submit to the DHMA. The DHMA receives and reviews the PSURs with decreasing frequency in the years following marketing of a drug. PSURs are reports, which update and summarize the safety status of a medicinal product and contains sections regarding all known ADRs, estimation of the number of treated patients, and an overall evaluation of the safety profile of the product. Furthermore, suggestions for new initiatives in regard to safety are described if relevant.[22]

The abovementioned is the work which is performed on a national level, however, there is also a lot of international cooperation in the work with pharmacovigilance at the DHMA, which ensures that information on safety is shared across countries. As mentioned earlier, international cooperation has been recognized to be important in pharmacovigilance.[9] One of the establishments for cooperation within the EU is the monthly meetings of the Pharmacovigilance Working Party (PhVWP). The PhVWP is a committee which evaluates safety related topics and issues recommendations in regard to safety for medicinal products on the European market. On the monthly meetings, where representatives from the EU countries, including Denmark, attend, the committee evaluates safety monitoring of drugs marketed in the EU and potential safety issues are discussed.[23] Another example of the cooperation within the EU is the European Pharmacovigilance Issues Tracking Tool (EPITT), which is a database, with the goal of promoting prompt communication regarding pharmacovigilance related issues between the European Medicines Agency (EMA), the PhVWP, national authorities, etc..[24] This means, that when safety signals are detected they can be communicated by means of the EPITT.

1.2.1 Development in pharmacovigilance at the Danish Health and Medicines Authority

The sources used by the DHMA for safety monitoring of marketed drugs are not all used equally and the DHMA would like to expand the use of some of the sources in order to be enhance the safety monitoring of drugs. A source which has begun to be used more in the recent years is the different national health registers. One of these is the Register of Medicinal Product Statistics (RMPS). This has been used e.g. when media or spontaneous reports on ADRs have indicated that there may be a safety issue with a drug which needs to be investigated further. The RMPS is a register owned and managed by the DHMA, in which information on the sales of medicinal products in Denmark has been recorded since 1994. This includes information on medicinal products sold on prescription, over-the-counter drugs, and drugs used for hospitalized patients. When a medicinal product is sold on prescription, around 30 different types of information are registered. This includes information related to the individual drug user, the medicinal

product, the prescriber, and the pharmacies. Besides from the information which is registered by the pharmacies etc., other information is also incorporated into the RMPS. This is information from the Danish Medicines Agency's Price List of Proprietary Medicinal Products, which contains information on e.g. Defined Daily Doses (DDDs) and Anatomical Therapeutic Chemical Classification System (ATC).[25] DDD is defined by the WHO as *"the assumed average maintenance dose per day for a drug used for its main indication in adults."*[26] The ATC classification system is a system where *"drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties."*[27] The register is the only register of its kind, containing data on redeemed prescriptions of an entire population over so many years and thereby holds unique opportunities in regard to investigating how and to what extent a drug is used in Denmark.[25]

The data available in the register offers the possibility to investigate some aspects of drug utilization for prescription drugs. These aspects include size and composition of the user population in regard to age and gender distribution, switch between drugs, and amount of redeemed drug in DDDs. By investigating these aspects it is possible to get a picture of how a drug is used and whether this changes over time. It is possible that the investigation can reveal safety issues, as e.g. skewed distribution patterns or changes in the patterns of use can be caused by reasons related to the safety of the drug. Furthermore, there might be statements in the SPC of a drug regarding the user population and contraindicated drugs and the investigation of utilization of a drug can possibly reveal whether these recommendations are adhered to. If they are not adhered to, this could be a safety issue. The suitability of the register for investigating the different aspects can depend on the drug being investigated. The register and its potential as a tool in safety monitoring is gaining increased interest at the DHMA and it is therefore relevant to investigate how the register can be used for safety monitoring and what needs to be considered when using the register for this purpose.

2 Aim

The aim of this study was to investigate whether and how methods for investigating the utilization of a drug by using dispensing data available in the RMPS can contribute to safety monitoring at the DHMA in the future. To investigate this, a drug was chosen as an example to perform the investigation of drug utilization on. For the example, the utilization of antidepressants with the active ingredient duloxetine (Cymbalta and Xeristar) was investigated. Antidepressants are a group of drugs which is used to treat the widespread disease major depression.[28] The aetiology of depression is very complex and the treatment is not always effective. There are a lot of controversies about the treatment with antidepressants and they are often subject to a lot of attention in regard to their effectiveness and safety.[28,29] Therefore, antidepressants were a relevant choice to perform the investigation on. The antidepressants Cymbalta and Xeristar are relatively new to the market as they were approved for marketing throughout the European Union for treatment of major depressive episodes in adults on the 17th of December 2004, and therefore constituted an example which it was interesting to perform the investigation on.[30]

The aspects of drug utilization which were investigated for Cymbalta and Xeristar were:

1. Size and composition of patient population
2. Patterns of drug use
3. Off-label use

3 Materials and methods

3.1 Study design and study population

This was a retrospective study using dispensing data to estimate the size and composition of the user population and the patterns of use of the antidepressants Cymbalta and Xeristar in the period 1st of January 2005 to 31st of December 2010. The study population consisted of all Danish residents who redeemed at least one prescription for Cymbalta or Xeristar within the study period. Through the study, Cymbalta and Xeristar were not distinguished between as they are two trade names of the same product and therefore the drugs are collected under the term Cymbalta/Xeristar.

3.2 Data sources

3.2.1 The Register of Medicinal Products Statistics

The dispensing data were retrieved from a register subset of the RMPS called Epikur, which is used for internal purposes at the DHMA only. The data available in Epikur is limited to data on redeemed prescriptions in the primary health sector and are cleared of returned transactions. In this study the information retrieved from Epikur on each patient included the encrypted civil registration number, age, gender, dates of redeemed prescriptions, redeemed amount of drug in DDDs, ATC code, and product number of the redeemed drug.

3.2.2 Medstat.dk

Medstat.dk is a website where the sales of drugs in Denmark can be found. It is based on data from the RMPS.[31] Medstat.dk was used to identify drugs containing duloxetine which were available on the Danish market in the years 2005-2010. The product numbers corresponding to other drugs than Cymbalta/Xeristar, in this case Yentreve, were identified.

3.2.3 Information on the drug

As mentioned, Cymbalta and Xeristar are two trade names of the same product and therefore their SPCs are identical. Therefore, the SPC of Cymbalta was used to obtain information on what the drugs were approved for in the study period (appendix B). Further, the information sheet ”Procedural steps taken and scientific information after the authorization” was used to obtain information on whether any changes relevant to this study were made in the SPC during the study period (appendix C).

3.3 Data collection and data analyses

In accordance with the aim of the study, the size and composition of the user population and the patterns of use of Cymbalta/Xeristar were investigated. The size and composition of the user population was investigated by identifying the overall number of users, number of naive users, which will be defined later, and the age and gender distribution of the users. The patterns of use was investigated by calculating the average amount of redeemed drug in DDDs per user, estimating the extent of switch from Cymbalta/Xeristar to other antidepressants, and estimating the extent of concomitant treatment with four contraindicated drugs. The extent of off-label use was investigated by looking in the SPC whether there were

any recommendations in regard to the aspects mentioned above and then comparing the results from the investigations to these recommendations.

In regard to age distribution the users were divided into the age groups '<18 years', '18-64 years', and '≥65 years'. This division was chosen based on the SPC where it is stated that Cymbalta/Xeristar should not be used in patients under the age of 18 years and that caution should be taken when treating patients aged 65 years or older (appendix B). The redemption of the prescription from which the age of the users was retrieved varied from analysis to analysis and will therefore be explained under each analysis. For all analyses, results were found for each calendar year.

Users of Cymbalta/Xeristar in this period were identified by retrieving data from Epikur by means of the ATC code 'N06AX21', corresponding to the active ingredient duloxetine. As the ATC code also includes the drug Yentreve, which was not indicated for the treatment of major depression, data on redeemed prescriptions for Yentreve was excluded from the analysis by means of the product numbers for Yentreve found on medstat.dk.

3.3.1 Size and composition of the user population

A user of Cymbalta/Xeristar was defined as a person who had redeemed at least one prescription for Cymbalta or Xeristar. A naive user was defined as a person who had not previously in the study period redeemed a prescription for either Cymbalta or Xeristar. The number of users was found by calculating how many persons had redeemed at least one prescription each year and the number of naive users per year was found by calculating how many persons had not previously redeemed a prescription.

To determine the distribution of the users across age groups and gender per year, the information on age group and gender was obtained from the first redeemed prescription of each user each year. Besides from the three overall age groups the age group '<18 years' were further subdivided into smaller groups. Users less than 18 years of age were each year appointed to one of the groups '<6 years', '6-10 years', '11-14 years', and '15-17 years'. This was done according to their age at the time of their first redeemed prescription each year.

3.3.2 Average redeemed amount of drug in DDDs per user

The average redeemed amount of drug in DDDs per user per year was calculated. Further, the average redeemed amount of drug in DDDs per user per year distributed on age group and gender was calculated. It is possible that a user changes age group between redeemed prescriptions within a year. In case of this, the total amount of drug in DDDs redeemed by the user in question that year was appointed to the age group which the user belonged to when redeeming the first prescription for Cymbalta/Xeristar that particular year.

3.3.3 Switch of drug to other antidepressants

Switch to other antidepressants was investigated as major depression is the main indication of Cymbalta/Xeristar. If the last redeemed prescription for Cymbalta or Xeristar was redeemed within 90 days before the first redeemed prescription for another antidepressant (table 1), this was considered a switch of treatment drug from Cymbalta/Xeristar to another antidepressant within same episode of depression (figure 2). In the SPC it is stated that it takes some time, around 2-4 weeks, before the effect of the drug set

Table 1. Categorization of other antidepressants used in this study.

Type of antidepressant	ATC code
Non-selective monoamine reuptake inhibitors	N06AA
Selective serotonin reuptake inhibitors	N06AB
Non-selective monoamine-oxidase inhibitors	N06AF
Monoamine-oxidase type A inhibitors	N06AG
Noradrenaline reuptake inhibitors	N06AX18
Serotonin and noradrenaline reuptake inhibitors	N06AX16
Noradrenergic and specific serotonergic antidepressants	N06AX03
	N06AX11
Melatonin agonists	N06AX22

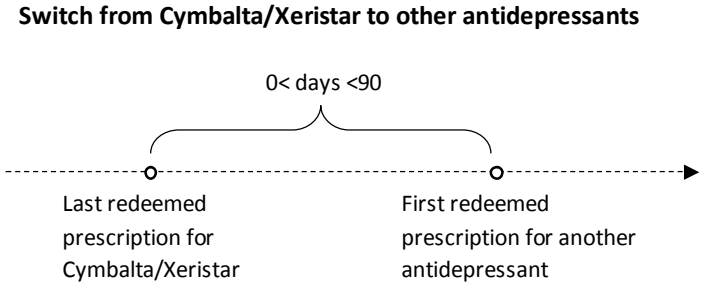

Figure 2. Definition of switch from Cymbalta/Xeristar to another antidepressant.

in. It is also stated that after an effect has been seen the treatment should continue for several months (appendix B). Having these recommendations in mind the period was set to 90 days.

In order to estimate the extent of switch, dispensing data on users of other antidepressants than Cymbalta/Xeristar was retrieved from Epikur by means of ATC codes of the other antidepressants (table 1). The dispensing data were retrieved from the period 1st of January 2005 to 31st of December 2010. The number of users who switch from Cymbalta/Xeristar to other antidepressants per year was found by means of the definition described above. The other antidepressants were considered one group and thereby the separate groups of antidepressants the users switched to were not found. To determine the composition of the user population who switch from Cymbalta/Xeristar to other antidepressants, the information on age group and gender was retrieved from the users' first redemption of a prescription for another antidepressant.

3.3.4 Concomitant treatment with contraindicated drugs

Concomitant treatment with Cymbalta/Xeristar was investigated for three drugs directly mentioned in the SPC as being contraindicated. In the SPC it was also stated that other drugs containing duloxetine should not be used concomitantly with Cymbalta/Xeristar (appendix B). This was also investigated and will also be referred to as a contraindicated drug.

Different definitions of concomitant treatment with contraindicated drugs were used dependent on the contraindicated drug in question. The contraindicated drugs were ciprofloxacin, fluvoxamine, other drugs containing duloxetine, and isocarboxazid (table 2). As mentioned, Yentreve was identified as the only other drug containing duloxetine in Denmark.

Table 2. Drugs contraindicated in treatment with Cymbalta/Xeristar.

Contraindicated drug	ATC code	Indications
Ciprofloxacin	J01MA02	Infections caused by bacteria sensitive to ciprofloxacin.[32]
Fluvoxamine	N06AB08	Moderate to severe depressive disorders.[33,34] Obsessive-compulsive disorder (OCD).[34]
Other drugs containing duloxetine (Yentreve)	N06AX21	Moderate to severe stress incontinence in females.[35,36]
Isocarboxazid	N06AF01	Depressive disorders that has not responded to other antidepressant treatment.[33,37]

It was considered concomitant treatment with Cymbalta/Xeristar and ciprofloxacin if one of the following scenarios were fulfilled (figure 3):

- A prescription for the contraindicated drug and a prescription for Cymbalta/Xeristar redeemed on the same date (figure 3a).
- A prescription for the contraindicated drug redeemed between two prescriptions for Cymbalta/Xeristar redeemed >0 and <90 days from each other (figure 3b).

It was considered concomitant treatment with Cymbalta/Xeristar and fluvoxamine, Yentreve, or isocarboxazid if one of the following scenarios were fulfilled (figure 3):

- A prescription for the contraindicated drug and a prescription for Cymbalta/Xeristar redeemed on the same date (figure 3a).
- A prescription for the contraindicated drug redeemed between two prescriptions for Cymbalta/Xeristar redeemed >0 and <90 days from each other (figure 3b).
- A prescription for Cymbalta/Xeristar redeemed between two prescriptions for the contraindicated drug redeemed >0 and <90 days from each other (figure 3c).

In order to estimate the extent of concomitant treatment with Cymbalta/Xeristar and ciprofloxacin, dispensing data on users of ciprofloxacin was retrieved from Epikur by means of the ATC code (table 2). The dispensing data were retrieved from the period 1st of January 2005 to 31st of December 2010. The number of users who fulfilled the scenario was found for each year. To determine the composition of the user population which was in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin the information on age group and gender was retrieved from the first time the users fulfilled the scenario within a year. If the first scenario fulfilled within a year was a scenario where three redeemed prescriptions were identified, information was retrieved from the midmost redeemed prescription. Besides from the three overall age groups, the users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin in the age group ’18-64 years’ were further subdivided into smaller groups by appointing users to one of the groups ’18-24 years’, ’25-34 years’, ’35-44 years’, ’45-54 years’, and ’55-64 years’.

In order to estimate the extent of concomitant treatment with Cymbalta/Xeristar and fluvoxamine, Yentreve, or isocarboxazid, dispensing data on users of the contraindicated drugs was retrieved from Epikur by means of the ATC codes (table 2). The dispensing data was retrieved from the period 1st of January 2005 to 31st of December 2010. The number of users who fulfilled any of the defined scenarios per year was found. To determine the composition of the user population which was in concomitant treatment with Cymbalta/Xeristar and fluvoxamine, Yentreve, or isocarboxazid the information on age group and gender was retrieved from the first time the users fulfilled a scenario within a year. If the first scenario fulfilled

within a year was a scenario where three redeemed prescriptions were identified, information was retrieved from the midmost redeemed prescription. Besides from the three overall age groups, the users in concomitant treatment with Cymbalta/Xeristar and Yentreve within the age group '18-64 years' were further subdivided into smaller groups by appointing users to one of the groups '18-24 years', '25-34 years', '35-44 years', '45-54 years', and '55-64 years'.

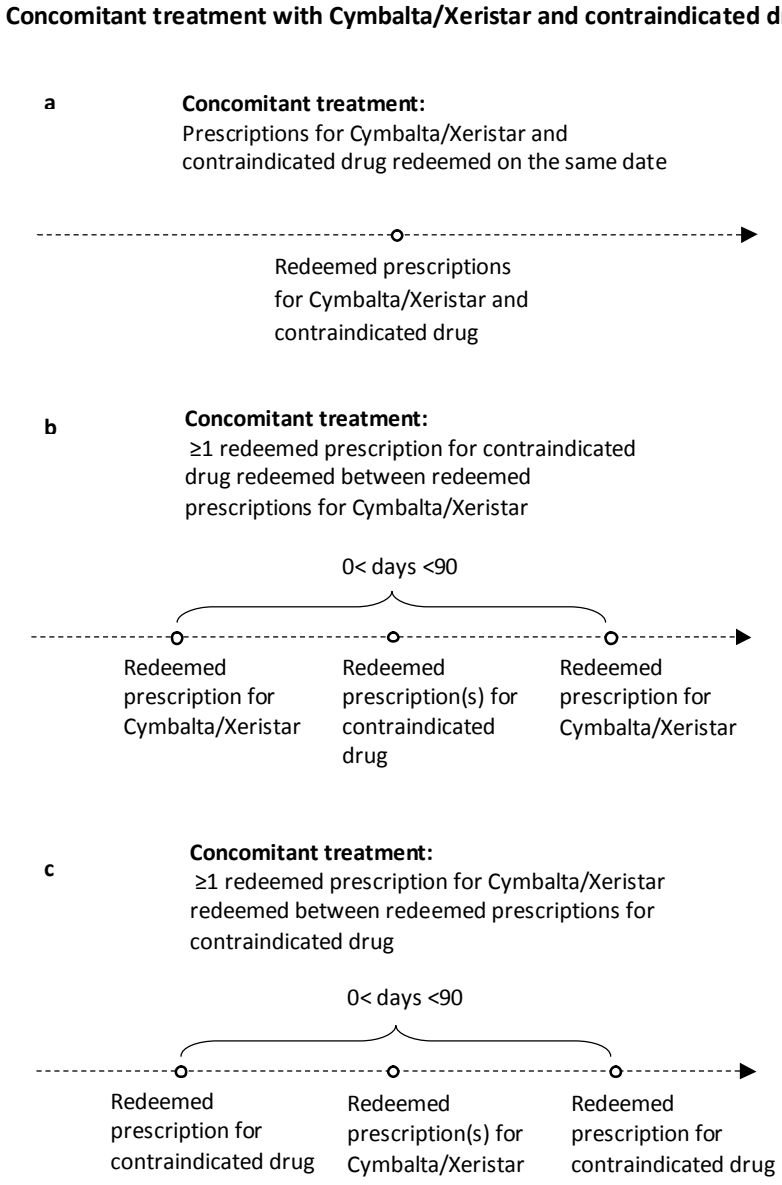

Figure 3. Scenarios used for identifying concomitant treatment with Cymbalta/Xeristar and contraindicated drugs. **a.** Prescriptions for Cymbalta/Xeristar and the contraindicated drugs redeemed on the same date. **b.** ≥1 prescription for contraindicated drug redeemed between two prescriptions of Cymbalta/Xeristar redeemed >0 and <90 days from each other. **c.** ≥1 prescription for Cymbalta/Xeristar redeemed between two prescriptions of the contraindicated drug redeemed >0 and <90 days from each other.

3.4 Statistics

Data retrieval and data handling were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2007 (Microsoft, Redmond, USA). In the appendix an example of SAS programs run in this study can be seen (appendix A). Descriptive statistics were performed. No statistical tests were performed as the whole population was available for the study.

3.5 Ethics

The study did not require approval from The National Committee on Health Research Ethics. As the dispensing data were anonymous there was no need to notify the Danish Data Protection Agency. The permission for accessing the data were given by the DHMA and the data retrieval were performed in-house.

4 Results

In this study it was found that there were users of Cymbalta/Xeristar of both genders and in all age groups in Denmark throughout the study period. Furthermore, it was found that the average of redeemed amount of drug in DDDs per user per year was increasing over the study period. It was also detected that some users switched to another antidepressant and that some were in concomitant treatment with contraindicated drugs.

4.1 Size and composition of the user population

The number of users of Cymbalta/Xeristar increased from year to year during the study period from a total number of users of 5,637 in 2005 to 21,464 in 2010. The greatest increase was seen between 2005 and 2006. The number of naive users per year was increasing each year from 2005 to 2008. From 2008 to 2010 the number decreased each year. Furthermore, the proportion of the total amount of users composed of naive users decreased every year throughout the study period. The annual distribution of number of users, the number of naive users, and the proportion constituted of naive users in percentages can be seen in figure 4.

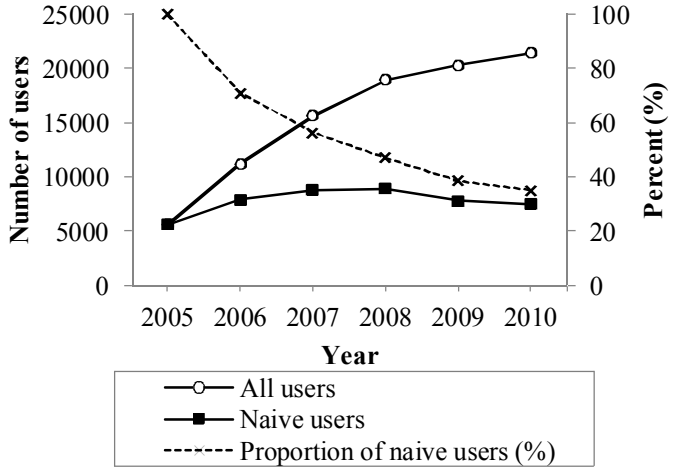

Figure 4. Overall number of users, number of naive users, and proportion constituted of naive users in percentages per year.

Table 3. Annual number of female and male users of Cymbalta/Xeristar.

Gender	Year					
	2005	2006	2007	2008	2009	2010
	N (% of total)					
Female	3753 (66.6%)	7630 (67.9%)	10731 (68.3%)	12931 (68.2%)	13864 (68.0%)	14574 (67.9%)
Male	1884 (33.4%)	3600 (32.1%)	4983 (31.7%)	6043 (31.8%)	6514 (32.0%)	6890 (32.1%)
Total	5637	11230	15714	18974	20378	21464

Table 4. Annual number of users of Cymbalta/Xeristar distributed on the three age groups.

Age (years)	Year					
	2005	2006	2007	2008	2009	2010
	N (% of total)					
<18	20 (0.4%)	43 (0.4%)	85 (0.5%)	87 (0.5%)	97 (0.5%)	97 (0.5%)
18-64	4755 (84.4%)	9420 (83.9%)	13168 (83.8%)	15790 (83.2%)	16784 (82.4%)	17560 (81.8%)
≥65	862 (15.3%)	1767 (15.7%)	2461 (15.7%)	3097 (16.3%)	3497 (17.2%)	3807 (17.7%)
Total	5637	11230	15714	18974	20378	21464

In the first study year, approximately two-thirds of the users were females. This distribution was almost constant during all years in the study period. Table 3 and figure 5 show the annual gender distribution of users.

In the first study year, the majority of users were found within the age group '18-64 years' followed by the age group '≥65 years' and the group with the least users were the age group '<18 years'. This age distribution remained the same throughout the study period. Table 4 and figure 6 show the annual distribution of users on the three age groups.

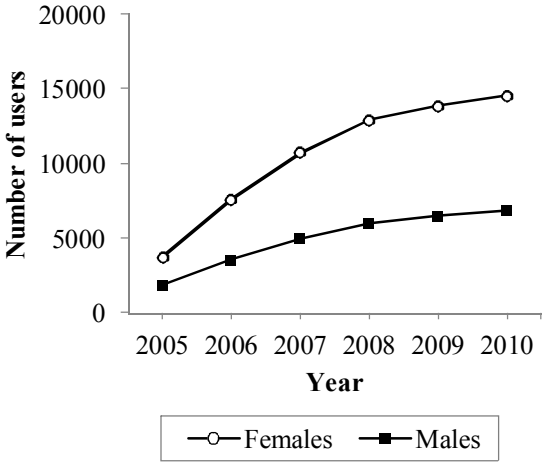

Figure 5. Annual number of female and male users.

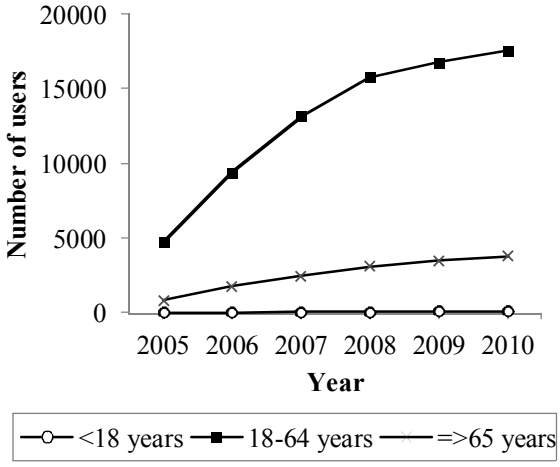

Figure 6. Annual number of users distributed on the three age groups.

Table 5. Annual distribution of female and male users in the three different age groups.

Age (years)	Gender	Year					
		2005	2006	2007	2008	2009	2010
		N (% of subtotal)					
<18	Female	18 (90.0%)	35 (81.4%)	68 (80.0%)	65 (74.7%)	71 (73.2%)	67 (69.1%)
	Male	2 (10.0%)	8 (18.6%)	17 (20.0%)	22 (25.3%)	26 (26.8%)	30 (30.9%)
	Subtotal	20	43	85	87	97	97,0
18-64	Female	3127 (65.8%)	6356 (67.5%)	8962 (68.1%)	10739 (68.0%)	11389 (67.9%)	11913 (67.8%)
	Male	1628 (34.2%)	3064 (32.5%)	4206 (31.9%)	5051 (32.0%)	5395 (32.1%)	5647 (32.2%)
	Subtotal	4755	9420	13168	15790	16784	17560
≥65	Female	608 (70.5%)	1239 (70.1%)	1701 (69.1%)	2127 (68.7%)	2404 (68.7%)	2594 (68.1%)
	Male	254 (29.5%)	528 (29.9%)	760 (30.9%)	970 (31.3%)	1093 (31.3%)	1213 (31.9%)
	Subtotal	862	1767	2461	3097	3497	3807
Total		5637	11230	15714	18974	20378	21464

For each study year it was found that the majority of users in all of the age groups were females. Table 5 shows the distribution of female and male users in the three different age groups.

In the first year of the study period, the majority of users less than 18 years were 15-17 years old. Throughout the study period, this age group accounted for ≥90% of the users less than 18 years of age. Table 6 shows the annual distribution of users less than 18 years of age distributed on four age groups.

Table 6. Number of users of Cymbalta/Xeristar <18 years of age distributed on four age groups per year.

Age (years)	Year					
	2005	2006	2007	2008	2009	2010
	N (% of total)					
<6	1 (5.0%)	1 (2.3%)	0 (0.0%)	1 (1.1%)	1 (1.0%)	0 (0.0%)
6-10	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
11-14	1 (5.0%)	3 (7.0%)	3 (3.5%)	6 (6.9%)	3 (3.1%)	4 (4.1%)
15-17	18 (90.0%)	39 (90.7%)	82 (96.5%)	79 (90.8%)	93 (95.9%)	93 (95.9%)
Total	20	43	85	87	97	97

4.2 Average redeemed amount of drug in DDDs per user

The results showed that the average redeemed amount of drug in DDDs per user was increasing every year throughout the study period. Figure 7 shows the annual number of users, overall annual redeemed amount of drug in DDDs, and the annual average of redeemed amount of drug in DDDs per user.

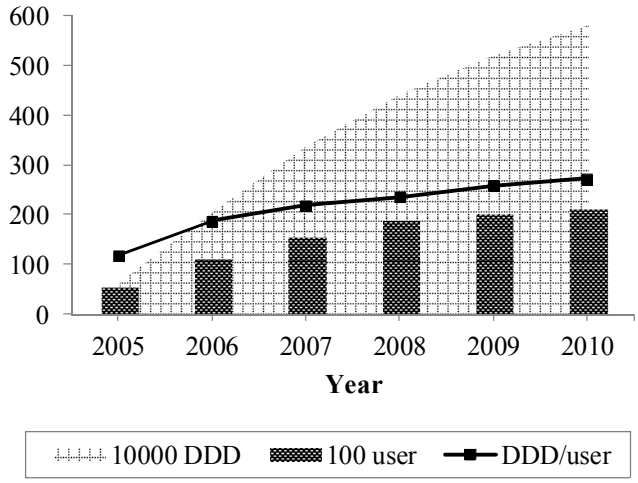

Figure 7. Annual number of users, overall annual redeemed amount of drug in DDDs, and annual average of redeemed amount of drug in DDDs per user.

It was seen that the annual average of redeemed amount of drug in DDDs per user was similar for females and males throughout the study period. The average amount per user increased every year for both genders. Figure 8 shows the annual average of redeemed amount of drug in DDDs per user distributed on gender.

In the first year of the study period, the annual average of redeemed amount of drug in DDDs per user was highest in the group '18-64 years', second highest in the group '≥65 years' and lowest in the group '<18 years'. This hierarchy consisted throughout the study period, except from 2006, where the value was higher for the group '<18 years' than for the group '≥65 years'. The average for the age groups '18-64 years', and '≥65 years' increased every year, whereas the average for the group '<18 years' increased from 2005 to 2006 followed by a decrease from 2006 to 2007. Hereafter the average increased every year throughout the rest of the study period. Figure 9 shows the annual average of redeemed amount of drug in DDDs per user distributed on the three age groups.

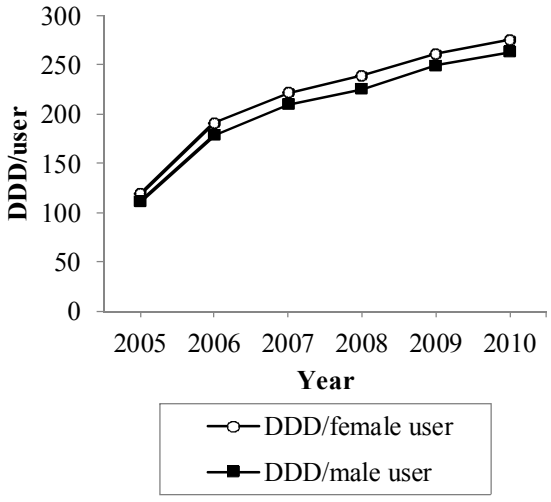

Figure 8. Annual average of redeemed amount of drug in DDDs per user distributed on gender.

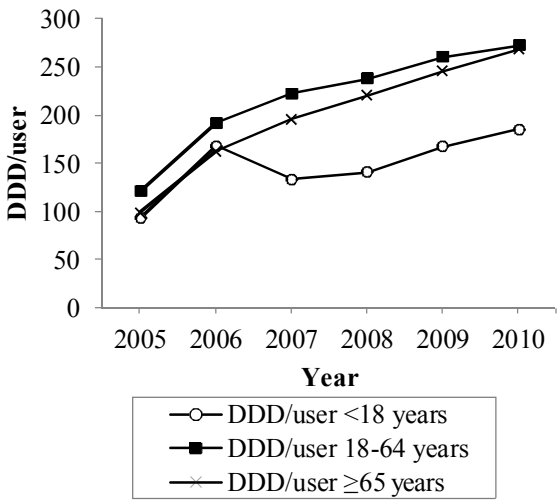

Figure 9. Annual average of redeemed amount of drug in DDDs per user distributed on age groups.

4.3 Switch of drug to other antidepressants

The number of users who switched from Cymbalta/Xeristar to other antidepressants within 90 days was found to be 152 in the first year of the study period. This corresponded to 2.7% of the total number of users that year. The proportion of users who switched in percentages of the total number of users was decreasing each year. Table 7 shows the number and proportion of users of Cymbalta/Xeristar who switched to other antidepressants. It was found that the distribution on gender and age groups for users who switched drug roughly resembled the gender and age distribution of the users in general.

Table 7. Annual number of users who switched from Cymbalta/Xeristar to another antidepressant within 90 days and the total number of users.

Days	**Year**					
	2005	**2006**	**2007**	**2008**	**2009**	**2010**
			***N* (% of total)**			
<90 days	152 (2.7%)	186 (1.7%)	222 (1.4%)	222 (1.2%)	224 (1.1%)	201 (0.9%)
Total	5637	11230	15714	18974	20378	21464

4.4 Concomitant treatment with contraindicated drugs

There were users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin throughout the study period. The number of users in concomitant treatment with the drugs was 41 in 2005, corresponding to 0.7% of the total number of users that year. The number increased every year throughout the study period to a number of 364 in 2010, corresponding to 1.7% of the total number of users that year. Table 8 shows the number of users of Cymbalta/Xeristar who were in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin.

Table 8. Annual number of users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin.

Contraindicated drug	**Year**					
	2005	**2006**	**2007**	**2008**	**2009**	**2010**
			***N* (% of total)**			
Ciprofloxacin	41 (0.7%)	124 (1.1%)	171 (1.1%)	262 (1.4%)	326 (1.6%)	364 (1.7%)
Total	5637	11230	15714	18974	20378	21464

The majority of users in concomitant treatment with ciprofloxacin were females and furthermore the majority was in the age group ’18-64 years’. Table 9 shows the number of users of Cymbalta/Xeristar who were in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin distributed on three age groups and gender.

As the majority of users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin were in the age group ’18-64 years’ this was further divided into smaller age groups to see more specifically how the users were distributed in this age group. It was found that throughout the study period the highest number of users was either in the group of females aged 45-54 years or females aged 55-64 years. Table 10 shows

Table 9. Annual number of users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin distributed on age groups and gender.

Age (years)	Gender	Year					
		2005	2006	2007	2008	2009	2010
		N(% of total)					
<18	Female	0 (0.0%)	0 (0.0%)	0 (0.00%)	1 (0.4%)	1 (0.3%)	1 (0.3%)
	Male	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.00%)	0 (0.0%)	0 (0.0%)
18-64	Female	21 (51.2%)	65 (52.4%)	79 (46.2%)	133 (50.8%)	156 (47.9%)	163 (44.8%)
	Male	7 (17.1%)	21 (16.9%)	36 (21.1%)	45 (17.2%)	59 (18.1%)	62 (17.0%)
≥65	Female	8 (19.5%)	25 (20.2%)	45 (26.3%)	56 (21.4%)	74 (22.7%)	84 (23.1%)
	Male	5 (12.2%)	13 (10.5%)	10 (5.9%)	27 (10.3%)	36 (11.0%)	54 (14.8%)
Total		41	124	171	262	326	364

the number of users of Cymbalta/Xeristar who were in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin in the age group '18-64 years' distributed on smaller age groups and gender.

Throughout the study period few users were in concomitant treatment with Cymbalta/Xeristar and fluvoxamine or isocarboxazid. The number was ranging from 2 to 5 users annually for fluvoxamine and 1 to 3 users annually for isocarboxazid. The annual number of users in concomitant treatment with Cymbalta/Xeristar and Yentreve was ranging from 55 to 160 users. Table 11 summarizes the number of users of Cymbalta/Xeristar who were in concomitant treatment with Cymbalta/Xeristar and fluvoxamine, Yentreve, or isocarboxazid.

Table 10. Annual number of users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin in the age group 18-64 years distributed on smaller age groups and gender.

Age (years)	Gender	Year					
		2005	2006	2007	2008	2009	2010
		N(% of total)					
18-24	Female	2 (7.1%)	3 (3.5%)	4 (3.5%)	8 (4.5%)	11 (5.1%)	9 (4.0%)
	Male	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	1 (0.5%)	1 (0.4%)
25-34	Female	4 (14.3%)	7 (8.1%)	10 (8.7%)	17 (9.6%)	20 (9.3%)	20 (8.9%)
	Male	2 (7.1%)	5 (5.8%)	7 (6.1%)	5 (2.8%)	6 (2.8%)	9 (4.0%)
35-44	Female	4 (14.3%)	16 (18.6%)	21 (18.3%)	26 (14.6%)	33 (15.4%)	24 (10.7%)
	Male	2 (7.1%)	4 (4.7%)	7 (6.1%)	7 (3.9%)	5 (2.3%)	13 (5.8%)
45-54	Female	6 (21.4%)	17 (19.8%)	18 (15.7%)	46 (25.8%)	40 (18.6%)	45 (20.0%)
	Male	1 (3.6%)	5 (5.8%)	7 (6.1%)	10 (5.6%)	21 (9.8%)	14 (6.2%)
55-64	Female	5 (17.9%)	22 (25.6%)	26 (22.6%)	36 (20.2%)	52 (24.2%)	65 (28.9%)
	Male	2 (7.1%)	7 (8.1%)	15 (13.0%)	20 (11.2%)	26 (12.1%)	25 (11.1%)
Total		28	86	115	178	215	225

Table 11. Annual number of users in concomitant treatment with Cymbalta/Xeristar and fluvoxamine, Yentreve, or isocarboxazid.

Contraindicated drug	Year					
	2005	2006	2007	2008	2009	2010
	N (% of total)					
Yentreve	55 (0.98%)	156 (1.39%)	151 (0.96%)	145 (0.76%)	160 (0.79%)	117 (0.55%)
Fluvoxamine	2 (0.04%)	3 (0.03%)	4 (0.03%)	5 (0.03%)	5 (0.03%)	3 (0.01%)
Isocarboxazid	3 (0.05%)	2 (0.02%)	1 (0.01%)	3 (0.02%)	3 (0.02%)	1 (0.01%)
Total	5637	11230	15714	18974	20378	21464

The majority of users in concomitant use with Yentreve were females. For both genders the majority was in the age group ’18-64 years’. Table 12 shows the number of users of Cymbalta/Xeristar who were in concomitant treatment with Cymbalta/Xeristar and Yentreve distributed on age groups and gender.

Table 12. Annual number of users in concomitant treatment with Cymbalta/Xeristar and Yentreve distributed on age groups and gender.

Age (years)	Gender	Year					
		2005	2006	2007	2008	2009	2010
		N(% of total)					
<18	**Female**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Male	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-64	**Female**	31 (56.4%)	93 (59.6%)	83 (55.0%)	82 (56.6%)	89 (55.6%)	73 (62.4%)
	Male	20 (36.4%)	42 (26.9%)	48 (31.8%)	44 (30.3%)	42 (26.3%)	29 (24.8%)
≥65	**Female**	4 (7.3%)	14 (9.0%)	16 (10.6%)	11 (7.6%)	24 (15.0%)	10 (8.6%)
	Male	0 (0.0%)	7 (4.5%)	4 (2.7%)	8 (5.5%)	5 (3.1%)	4 (3.4%)
Total		55	156	151	145	160	117

As the majority of users in concomitant treatment with Cymbalta/Xeristar and Yentreve were in the age group ’18-64 years’ this was further divided into smaller age groups to see more specifically how they were distributed on age and gender. It varied from year to year in which of the groups the highest number of users was found. Table 13 shows the number of users who were in concomitant treatment with Cymbalta/Xeristar and Yentreve in the age group ‘18-64 years’ distributed on smaller age groups and gender.

Table 13. Annual number of users in concomitant treatment with Cymbalta/Xeristar and Yentreve in the age group 18-64 years distributed on smaller age groups and gender.

Age (years)	Gender	Year					
		2005	2006	2007	2008	2009	2010
		N(% of total)					
18-24	Female	1 (1.96%)	4 (2.96%)	6 (4.58%)	3 (2.38%)	10 (7.63%)	4 (3.92%)
	Male	0 (0.0%)	0 (0.0%)	3 (2.29%)	4 (3.17%)	3 (2.29%)	2 (1.96%)
25-34	Female	7 (13.73%)	13 (9.63%)	18 (13.74%)	11 (8.73%)	16 (12.21%)	20 (19.61%)
	Male	5 (9.80%)	9 (6.67%)	8 (6.11%)	8 (6.35%)	4 (3.05%)	5 (4.90%)
35-44	Female	8 (15.69%)	22 (16.30%)	29 (22.14%)	23 (18.25%)	23 (17.56%)	21 (20.59%)
	Male	8 (15.69%)	10 (7.41%)	8 (6.11%)	7 (5.56%)	12 (9.16%)	7 (6.86%)
45-54	Female	8 (15.69%)	27 (20.00%)	10 (7.63%)	36 (28.57%)	25 (19.08%)	17 (16.67%)
	Male	5 (9.80%)	14 (10.37%)	19 (14.50%)	7 (5.56%)	12 (9.16%)	7 (6.86%)
55-64	Female	7 (13.73%)	27 (20.00%)	20 (15.27%)	9 (7.14%)	15 (11.45%)	11 (10.78%)
	Male	2 (3.92%)	9 (6.67%)	10 (7.63%)	18 (14.29%)	11 (8.40%)	8 (7.84%)
Total		51	135	131	126	131	102

5 Discussion

In the present study the use of Cymbalta/Xeristar in Denmark was investigated by using dispensing data available in the RMPS. This was performed in order to investigate whether and how an investigation like this can contribute to safety monitoring in the future. To the knowledge of the authors an investigation like this has not previously been performed. In the following the results from the investigation, considerations about the methods, and ideas about whether such an investigation can contribute to safety monitoring at the DHMA in the future is discussed. The main focus is on safety, however, other aspects is briefly touched.

5.1 Findings

The results from the investigation of the utilization of Cymbalta/Xeristar may identify overall tendencies and distribution patterns which may constitute potential safety issues for the user population. There is no golden standard for determining whether there are safety issues or not. It can vary from drug to drug what is considered a safety issue and therefore safety issues of the drugs cannot be revealed by simply assessing whether the results exceed a certain value or proportion. Rather the results should be evaluated while bearing existing knowledge on the drugs in mind.

5.1.1 Size and composition of the user population

Overall number of users

In the study the size of the user population of Cymbalta/Xeristar was investigated. The number of users of Cymbalta/Xeristar increased from 2005 to 2010. The increase was greatest in the beginning, after which it

diminished from year to year. This seems as a natural development, when considering that 2005, the first study year, was the first year with purchases of Cymbalta/Xeristar after marketing. It can be argued that after marketing of a drug, it may take some years for the drug to find its place on the market and therefore the number of users will increase in the first years. When a drug is first marketed it might be expected that the drug will have a more tolerable safety profile and a better effect than the drugs already on the market for the same indications. This may lead physicians to prescribe the new drug to patients. The fact that the number of users of Cymbalta/Xeristar continuously increases may indicate that the physicians have had good experiences with the drugs and therefore continue to prescribe them. An increase in the number of users of a drug can also be due to that the drug in question is approved for new indications. All drugs on the Danish market can in theory be prescribed for any indication, regardless of whether the drug is approved for this, as physicians are allowed to prescribe drugs for any indication if they have estimated that it is the best drug for the particular patient.[38] However, it is reasonable to assume that drugs are most often prescribed for what they are recommended for. Therefore, once a drug is approved for additional indications it would possibly lead to a larger number of users of that drug as it is approved for use in a larger population. Cymbalta/Xeristar were initially approved for the treatment of major depression. Later the indications were extended to also include treatment of diabetic peripheral neuropathic pain in 2005, treatment of generalized anxiety disorder in 2008, and prevention of recurrent episodes of major depression in 2009 (appendix C). Therefore, it is possible that the introduction of these new indications had a contributing factor in the increasing number of users of Cymbalta/Xeristar throughout the study period.

When looking at the number of naive users, it is seen that the number was roughly constant over the years in the study period whereas the total number of users increased each year. Thereby, the naive users constituted a gradually smaller proportion of the total number of users each year. This means that many of the users who initiated treatment with Cymbalta/Xeristar continued this treatment over the study years or were in recurrent treatment. In regard to safety of the drugs these results can be interpreted as positive, as they indicate that the treatment, at least for some users, was satisfactory. If the treatment had not been satisfactory, it is not likely, that the users would stay in treatment with the drug over a longer period or return to treatment with the same drug. Thereby, the users would not appear as users in the following study years. However, it depends on the severity of the disease, which the drug in question is typically used in the treatment of, whether some degree of ADRs can be accepted. It also depends on whether there are other drugs available on the market to treat the specific disease or if there are no other alternatives. In the case of Cymbalta/Xeristar there were several other drugs available for the indication of major depression throughout the study period.[33] This support the assumption that patients treated with Cymbalta/Xeristar were generally satisfied with the treatment, as there were other alternatives for the main indication.

In summary, the fact that the number of users of Cymbalta/Xeristar was continuously increasing and the proportion of naive users was decreasing over the study years does not indicate any potential safety issues.

Number of users distributed on gender

The results showed that throughout the study period approximately two-thirds of the users were females. When evaluating the results, it is reasonable to compare the gender distribution of the users to the gender distribution of the patients suffering from the diseases, which the drugs are indicated for to see if the patterns of gender distribution are similar or not. If these distributions are not similar, it might indicate that the drug in question is not effective or may have safety issues in one of the genders. The prevalence of

major depression is twice as high in women as in men and women are also more frequently affected by generalized anxiety disorder than men.[39,40] For diabetic peripheral neuropathic pain the prevalence is equal for the genders.[41] Since the prevalence of the diseases is either equal for the genders or more prevalent in females, it does not seem surprising that there were more female users than male users. Due to this and that the pattern was not changing over time, no potential safety issue connected to one of the genders was detected.

Number of users distributed on age groups

The use of Cymbalta/Xeristar in the two age groups '18-64 years', and '≥65 years' does not indicate any potential safety issues, as the drugs were approved for these ages and thereby it could be expected that there were users of the drugs in these age groups (appendix B). The majority of users of Cymbalta/Xeristar in the study period belonged to one of these age groups. However, the study revealed that there were also users below 18 years of age throughout the study period. This could possibly be a potential safety issue as it was stated in the SPC that Cymbalta/Xeristar should not be used in patients under 18 years of age (appendix B). To investigate this further, the age distribution of the users under 18 years of age was investigated. It was found that the majority of users under 18 years of age were adolescents in the group of 15-17 year olds. It can be argued that adolescents are physiologically closer to adults, for whom the drugs are approved, than young children are. Thereby, the use of the drugs in adolescents may constitute less of a safety issue than the use of the drugs in young children. Furthermore, it is a fact that major depression does not only appear in adults, but also in children and adolescents and therefore they also need treatment for the disease.[42] From 2006, the antidepressant fluoxetine has been approved for use in children suffering from major depression.[43] However, as there are different individual clinical needs, there may be cases where other antidepressants not approved for use in children were considered a better choice of treatment. Thus, it is not surprising, and can possibly not be avoided, that there were a number of children and adolescents in treatment with antidepressants not approved for use in children, in this case Cymbalta/Xeristar. Having the above mentioned considerations in mind, it can be argued that the relatively low number of users under 18 years of age, constituting a maximum of 0.5% of the users per year, did not constitute a safety issue.

5.1.2 Average redeemed amount of drug in DDDs per user

The results showed that the annual average of redeemed amount of drug in DDDs per user was increasing from year to year in the study period. This indicates that either the users were in longer treatment with Cymbalta/Xeristar or the treatment dose was increased. It is also possible that it was a combination of the two. This analysis does not reveal what caused the increase. As it is possible that there could be different patterns for the different age groups and gender which cannot be revealed by the overall average, the annual average of redeemed amount of drug in DDDs per user of each gender and age groups was investigated.

The annual average of redeemed amount of drug in DDDs for female and male users was seen to be almost equal each year in the study period. This could be interpreted as positive results as they at a glance indicate that the treatment with Cymbalta/Xeristar did not vary between females and males according to dose and duration of treatment. However, it should be noted that the patterns seen could hide differences between females and males in regard to dose and duration of treatment. E.g. a high dose and short duration of treatment in one gender and a low dose and long duration of treatment in the other gender could

balance each other and give the same result in regard to average redeemed amount of drug in DDDs per user.

The annual average of redeemed amount of drug in DDDs is almost equal for the age groups ’18-64 years’ and ‘≥ 65 years’. As with the distribution on gender it is possible that the pattern seen can hide differences between the two groups in regard to dose and duration of treatment. However, when looking at the overall differences between the two groups, it could be argued that it seems rational that the average for the age group’18-64 years’ is slightly higher than the average for the age group ‘≥ 65 years’, since it is stated in the SPC that users at the age of 65 years or older should be treated with caution. The pattern for the average for the age group ‘<18 years’ separates from the pattern for the average for the two other age groups, when the average decreases from 2006 to 2007. This means that from 2007 and forward, either the treatment dose, duration of treatment, or both is lower in the age group ‘<18 years’ than the two other age groups. When looking at these results it should be noted that as the number of users in the age group ‘<18 years’ is relatively low, changes in DDDs for individual users affect the results more than when the average is calculated from a large number of users. Therefore, the results for this age group can be subject to greater variation. It is, however, still possible to look at the tendencies of the groups. Cymbalta/Xeristar are not approved for treatment of children and adolescents. As the average for this group was lower, it could be interpreted as a positive result in regard to safety, as it indicates that the prescribers are more cautious when treating this group of patients.

5.1.3 Switch of drug to other antidepressants

It was found that there were some users who switched from Cymbalta/Xeristar to other antidepressants. This could indicate that these patients may have experienced intolerable ADRs or lack of effect of the drugs. The results showed that through all the study years the number of users who switched constituted only a small proportion of the total amount of users, the highest value being 2.7% in 2005. The number itself does not seem to reveal any potential safety issues, as it can be argued that there for all drugs always will be a small fraction of people who find that the treatment with a drug they are using is not satisfactory and therefore switch to another drug. However, it is possible that all the users who switched were within one specific age group or gender, which could indicate safety issues in these groups. Therefore, the distribution should be taken into consideration before concluding anything. In this study the age and gender distribution of the users reflected the general distribution of the users and therefore it did not reveal any age or gender specific safety issues. Based on the patterns seen in this analysis, there were no alarming results which indicated a potential safety issue.

5.1.4 Concomitant treatment with contraindicated drugs

The results showed that there were some users in concomitant treatment with Cymbalta/Xeristar and each of the contraindicated drugs ciprofloxacin, fluvoxamine, Yentreve, and isocarboxacid. These results could all reflect potential safety issues for the individuals in concomitant treatment. However, as mentioned earlier, this investigation aims to detect whether there are tendencies which indicate general safety issues and not safety issues for individuals. Furthermore, it can be argued that there might be cases where concomitant treatment with the contraindicated drugs are necessary, e.g. due to lack of alternative drugs or individual clinical needs. Therefore, the few users in concomitant treatment with Cymbalta/Xeristar and fluvoxamine or isocarboxacid do not seem to reveal any alarming tendencies.

Concomitant treatment with Cymbalta/Xeristar and ciprofloxacin was found to be increasing with a higher rate than the overall number of users of Cymbalta/Xeristar over the years in the study period. This could indicate a potential safety issue, since there is a clear tendency that the proportion of users in concomitant treatment was increasing. In regard to the distribution on age groups and gender, the users in concomitant treatment with Cymbalta/Xeristar and ciprofloxacin were widely distributed over age groups and genders, indicating that the safety issue could not be ascribed to a specific age group or gender. As mentioned, there may be reasons for prescribing contraindicated drugs such as lack of alternative treatment options. It is possible that other drugs can be alternatives to ciprofloxacin. As ciprofloxacin is an antibiotic, there might be resistance problems which make ciprofloxacin the best choice of treatment for some conditions. In Denmark there has generally been a restricted use of antibiotics and thereby there have been few problems with resistance, however, both the use of antibiotics and the problems with resistance is increasing, which result in that the number of drugs available for treating some diseases are reduced.[44] In the study period there were various alternatives to Cymbalta/Xeristar for its main indication major depression and it is thereby possible that concomitant treatment could have been avoided. However, it can be argued that there might be cases where it is evaluated that there is a greater risk for the patient in switching to another antidepressant than treating the patient concomitantly with ciprofloxacin. With that said, the proportion of users in concomitant treatment with ciprofloxacin was increasing over the years and this is an alarming tendency which constitutes a potential safety issue.

Concomitant treatment with Cymbalta/Xeristar and Yentreve was detected, which could constitute a potential safety issue. When investigating the distribution of users on age groups and gender it was seen that the users were not within a specific age group or gender, indicating that the safety issue could not be ascribed to one particular group. As mentioned, there might be reasons for prescribing contraindicated drugs concomitantly. However, the detected concomitant use with Cymbalta/Xeristar and Yentreve seem irrational as Yentreve contains the same active ingredient as Cymbalta/Xeristar. It makes no sense to prescribe two drugs with the same active ingredient concomitantly, even if they were prescribed for different indications. Therefore, the concomitant treatment with Cymbalta/Xeristar seems irrational and constitutes a potential safety issue.

5.1.5 Summary of findings

For the size and composition of the user population of Cymbalta/Xeristar, average redeemed amount of Cymbalta/Xeristar in DDDs per user, switch from Cymbalta/Xeristar to other antidepressants, concomitant treatment with Cymbalta/Xeristar and the contraindicated drugs fluvoxamine and isocarboxazid, the results did not reveal any potential safety issues. On the contrary, the detected concomitant treatment with the contraindicated drugs ciprofloxacin and Yentreve was found to constitute potential safety issues.

5.2 Strengths and limitations

In the investigation of the utilization of Cymbalta/Xeristar it was found that it was possible to detect potential safety issues by means of the methods using dispensing data from the RMPS. The methods have both strengths and limitations. This also applies to the RMPS as a data source. The strengths and limitations of both the RMPS and methods used in this study for assessing drug utilization are discussed in the following.

5.2.1 Data Source

In this study data from the RMPS was used for investigating the consumption of a drug. A strength connected to this is that the data in the register is considered to be of high completeness and validity.[45] Compared to medical records and surveys, the data are considered more complete as the collection of the information is required by law in Denmark.[25,46] Furthermore, dispensing data has an advantage, as the risk of selection bias or recall bias, which are present in surveys, is eliminated.[46] The RMPS contains information on redeemed prescriptions of the whole Danish population since the register was established, which makes it unique in regard to investigating the drug utilization across the nation over time.[25]

There are also limitations connected to using the RMPS. When using a dispensing register for investigating the consumption of a drug, it must be taken into consideration that the register contains information on redeemed prescriptions and not on the actual consumption of drugs of the persons who redeem the prescriptions. In this study, the redeemed prescriptions therefore function as proxies for consumption, as it is assumed that persons who purchase the prescription drugs also ingest them. The fact that there is no assurance that the persons ingest the drug they have collected at the pharmacy is a limitation. This limitation has also been recognized in other studies using dispensing data for investigating use of a drug.[47-50] The person purchasing the drug might even distribute the drug to others. Therefore, the results found by using the register are estimations and should be processed bearing this in mind.

5.2.2 Size and composition of the user population

The method for determining size and composition is strong as it is not based on any assumptions besides from the previous mentioned assumption, which applies to all the methods, that persons who redeem a prescription for a drug are consuming the drug. There is no uncertainty about either the gender or the age of the users, as this information is registered each time a prescription is redeemed and thereby this information can be readily retrieved from the RMPS. As a part of the method, each user is only counted once each study year. It is likely that many users have birthday in between prescriptions redeemed within the same year. Therefore, it should be chosen whether the users' age at the time of the first redeemed prescription of the year or the last redeemed prescription of the year should be retained. Even though this does not constitute a strength or limitation, it should be noted that the results depend on whether the one or the other option is chosen.

In the example the users were split into age groups. Which age groups the users should be split into can depend on the drug being investigated and what the aims of the investigation are. There might be statements in the SPC in regard to specific age groups and this could form the basis of the subdivision into age groups, which was the case in this example. It is also possible that it is wanted, for some reason, to highlight a certain age group and in this case the age groups could be formed on the basis on this.

5.2.3 Average redeemed amount of drug in DDDs

The method for determining average redeemed amount of drug in DDDs per user each year in itself can be considered a strong method. This is due to that it is not based on any assumptions besides from the previous mentioned assumption that persons who redeem a prescription for a drug ingest the drug. Thereby, it provides reliable results for the average redeemed amount of drug in DDDs per user each year, both overall and distributed on age groups and gender. The method can reveal changes in this over time which could be a result of changes in dose, treatment duration, or both. However, a great limitation of the method is that it cannot be determined which of the mentioned factors is the reason for the change. Also,

changes in the factors, e.g. a decrease in dose and increase in treatment duration, could balance each other and thereby not be revealed in the results. Furthermore, when looking at variations in the average over the years, the size of the group which the average is calculated from should be taken into consideration. This is due to that the redeemed amount of drug in DDDs per user has a larger influence on the results when calculated from a low number of users than when calculated from a large number of users. That is, changes in DDDs for individual users can lead to great variations in the average when calculated from a low number of users and this should be considered when evaluating the results.

In summary the method in itself is strong. However, when evaluating the results in regard to safety, caution should be taken before drawing any conclusions since the results can hide different patterns of use.

5.2.4 Switch of drug

The method for determining switch enables identification of potential safety issues of a drug as a switch could be caused by e.g. ADRs or lack of effect. However, the method is connected with some limitations. Contrary to the methods discussed above, the method is based on more assumptions.

The method consists of identifying users where the last redemption of the drug being investigated and the first redemption of the drug(s) to which the patients might switch lies within a certain time interval. The strength of using this method is that it avoids identifying users who are in concomitant treatment with the drugs rather than users who are switching between them. It could be argued that there can be cases where a user switches from a drug to the drug being investigated and then switches back to the first drug again. In these cases the switch would not be identified when using this method. However, it does not seem likely that a patient switches from one drug to another and then switches back to the first again, at least not for drugs treating a disease, for which there are numerous drugs to choose from. If patients switch forth and back more times, it can be argued that the reason for the switch is most likely not a great safety issue, otherwise they would probably not switch back to the drug.

In the case with Cymbalta/Xeristar, it was investigated how many users switched from Cymbalta/Xeristar to another antidepressant. For the treatment of major depression there are many alternatives to Cymbalta/Xeristar, and therefore the scenario where a user switch from one antidepressant to Cymbalta/Xeristar and then back to the first antidepressant, was not as likely to happen as if only a few alternatives had been available.[33] Therefore, it can be argued that the method in regard to this matter would give a reasonable estimate of switch for the example of Cymbalta/Xeristar.

The method for estimating switch of drug is also based on another assumption. When determining switch it is necessary to define a period within which the drugs, between which the switch is investigated, should be redeemed in order for it to be interpreted as a switch. There is no golden standard for setting the period. Therefore, when determining the length of the period, the specific drug being investigated should be taken into consideration. The period can be determined by considering how the normal course of treatment with the drug in question is in regard to duration. If the drug being investigated is e.g. a drug used in the treatment of a chronic disease, the period can be long, as the patients are most likely in continuous treatment for their disease. If it, on the other hand, involves a drug which is used for more acute and short-term treatment, it would be more rational to set a short period. The longer the period is, the greater the risk is that it is not necessarily a switch which is identified, but rather that the user is ending one treatment for one disease and starting another treatment for another disease or even a new round of the same disease. On the contrary, the shorter the period is, the greater the risk is that not all users who switch

are identified. It is attempted to avoid these cases by setting the period as best as possible. However, as treatment is very individual, there is no assurance that all users who are identified as users switching drug are actually switching drug. Nor is there any assurance that all users who switch drug are identified and this is a limitation of the method, in some cases more pronounced than others.

In the example with Cymbalta/Xeristar, the period for determining switch was set to 90 days. It is possible that more users would have been identified, if a longer period was chosen. However, if a longer period was chosen, there would be a greater uncertainty as to what was included in the results, as discussed above. It can be argued that 90 days is a reasonable period for determining switch between antidepressants, when assuming that they are prescribed for treating major depression, as the duration of the treatment for this disease is normally of longer duration (appendix B). Therefore, if redemption of an antidepressant is followed by redemption of a second antidepressant within the period of 90 days, it is most likely that the second antidepressant is used to treat the same episode of depression, rather than a new episode of depression.

It should be noted that Cymbalta/Xeristar are also indicated for treating other conditions than major depression. In the example, switch was investigated for the main indication of Cymbalta/Xeristar, i.e. major depression. It is possible that there were some users in treatment with Cymbalta/Xeristar for one of the other indications and if these users switched to another drug for that indication, it would not be detected through this method. Thereby, the actual number of users who switched drug may be larger. However, the number of users who switched to another antidepressant is considered a reasonable estimate of the actual number of users who switched between drugs for this indication, since the period was set based on the typical treatment course of this disease.

In summary, the method for investigating switch is connected to some strengths and limitations. The number of users identified as users who switch may be an over- or underestimation of the actual number of users who switch. However, when adjusting the method to the drugs being investigated, it can provide a reasonable estimate of the number of users who switch.

5.2.5 Concomitant treatment with contraindicated drugs

The method for determining concomitant treatment with contraindicated drugs enables potential safety issues of a drug to be identified. However, the method is also connected with some limitations as it is based on assumptions similar to the ones explained for the method for estimating the extent of switch.

The method consists of identifying the users who fulfill scenarios set for the specific drug being investigated. The first scenario, which can be applied for all drugs, is redeemed prescriptions of the drug being investigated and redeemed prescriptions of the contraindicated drugs redeemed on the same date. It can be argued that the probability of this scenario being concomitant treatment is high. If two prescriptions are redeemed on the same date, it is natural to assume that they are redeemed with the intention of ingesting both drugs concomitantly. Therefore, this part of the method can be argued to be of high validity. However, if this is the only scenario considered concomitant treatment, the number of users is most likely underestimated as concomitant treatment can also happen, even though the prescriptions are not redeemed on the same day. The risk of underestimation has also been recognized in a study by Zoëga and colleagues who identified prescriptions redeemed on the same date to investigate concomitant treatment.[50] Additionally, Tobi and colleagues who investigated the impact of definitions of concomitant treatment argued that different definitions are appropriate for different types of studies. They argued that when in-

vestigating safety concerns, where high sensitivity is important, it is not sufficient to identify prescriptions redeemed on the same date.[51] Therefore, this method also included scenarios where 3 prescriptions should be redeemed within a certain period of time, but not on the same date. That is, two redeemed prescriptions of the drug being investigated redeemed within a certain period and one redeemed prescription for the contraindicated drug redeemed on a date in between the two redeemed prescriptions of the drug being investigated, or the other way around. The advantage of identifying three redeemed prescriptions is that it avoids identifying users who switch as users in concomitant treatment. It can be argued that if only one redeemed prescription for the drug being investigated and one redeemed prescription for the contraindicated drug are identified there is a risk of identifying patients who was not in concomitant treatment but rather has ended treatment with the drug being investigated and started treatment with a contraindicated drug afterwards or the other way around. The scenario of three redeemed prescriptions can, however, not necessarily be applied for all drugs which is a limitation of the method. It depends on the drug being investigated and the contraindicated drugs how suitable this part of the method is. This is due to that it is necessary to set a period within which the prescriptions should be redeemed in order for it to be considered concomitant treatment and it is not always possible to set a reasonable period for all drugs. To set the period, the typical course of treatment with the drugs in question should be considered. If the normal treatment with a drug is of longer duration, the period set can be relatively long, as it is not likely that users stop the treatment in between prescription. On the other hand, if it is a drug which is normally used for short term treatment, e.g. 7 days, it would be irrational to set the period to e.g. 90 days, as the likelihood of it being two rounds of treatment and not continuous treatment is high.

In the example with Cymbalta/Xeristar it was demonstrated that not all of the scenarios were suitable for estimating concomitant use with the contraindicated drug ciprofloxacin. Ciprofloxacin is an antibiotic for which the length of treatment can vary from a few days to several months.[52] Because of these varying lengths of treatment, it was not possible to set a reasonable period and therefore the scenario which would be redeemed prescriptions of ciprofloxacin-Cymbalta/Xeristar-ciprofloxacin was not applied. This constitutes a limitation since it is possible that the exclusion of this scenario causes an underestimation of the users in concomitant treatment with ciprofloxacin.

For the other contraindicated drugs, the period was set to 90 days. As the remaining contraindicated drugs were all typically used for long term treatment, it seemed reasonable to set this period for both of the scenarios where three redeemed prescriptions are identified. Thereby, the limitation mentioned for the method for investigating concomitant treatment with ciprofloxacin, where only one of the scenarios where three prescriptions are redeemed could be applied, does not apply when using the method for the contraindicated drugs Yentreve, fluvoxamine, and isocarboxazid in this example.

In summary, the method for investigating concomitant treatment is based on assumptions and therefore the number of users identified as users in concomitant treatment may be an over or underestimation of the actual number of users in concomitant treatment. Still, the method for estimating concomitant treatment with contraindicated drugs constitutes a useful method when adjusted to the drugs being investigated.

5.3 Future prospects

As demonstrated in the example with Cymbalta/Xeristar, the methods using data from the RMPS offer the possibility to estimate the utilization of drugs and based on this investigate whether there are overall tendencies, which may seem alarming and constitute a potential safety issue. As the RMPS contains data

on all prescription drugs redeemed in Denmark, the utilization of any prescription drug marketed in Denmark can be investigated. In regard to using the methods for other drugs than Cymbalta/Xeristar, it is important to recognize that the methods should be adjusted to the drug being investigated and that when evaluating the results, the influence of the choices made when planning the analyses should be considered. Future prospects for using investigations as the one demonstrated in this study as a tool for safety monitoring by the DHMA are discussed in the following. Furthermore, initiatives which would make it possible to investigate additional aspects of drug utilization are suggested.

Performing an investigation of the utilization of a drug offers an additional approach for safety monitoring of drugs by the DHMA. It constitutes an inexpensive approach, which is easily accessible for the DHMA. In regard to this, it should be noted that the applied methods have some limitations. This, however, applies to all methods used in pharmacovigilance. None of the sources and methods in pharmacovigilance is ideal and therefore it can be an advantage to use different sources and methods as they can possibly compensate for the limitations of each other.

The investigations of drug utilization can both be performed retrospectively as demonstrated in this study and prospectively. Retrospective studies offer the possibility of investigating how the utilization of a drug has been in a defined period whereas prospective studies offer the possibility of following the utilization of a drug as it develops. That is, in prospective studies data are collected continuously as it becomes available enabling potential safety issues to be detected as they arise. It depends on the reasons for initiating an investigation which of the two study designs are best suited for the investigation.

In their work with safety monitoring, the DHMA could have different reasons for initiating an investigation of the utilization of a drug as the one performed in this study. For example it is possible that the DHMA chooses to monitor the utilization of a new drug prospectively if it is thought that the drug will be widely used or are in a group of drugs in which experience has shown that safety issues often arises. Another reason for initiating an investigation could be if a suspicion of a safety issue arises and needs to be followed up. This could e.g. be a suspicion about a drug being increasingly used in an age group for which it is not indicated or that drugs which should not be used concomitantly due to safety reasons, are used concomitantly. This could be investigated by applying the methods demonstrated in this study. It is possible that an investigation as the one performed in this study can also be used to evaluate whether there is an effect of initiatives taken by the DHMA, e.g. whether changes made to the SPC are adhered to.

As mentioned, when applying the methods for other drugs the methods should be adjusted to the drug in question. In addition to this, one might consider to leave out some of the methods used in this example. This is due to that some of them, as discussed earlier, can be more applicable for some drugs than others. It could also be possible to add other analyses depending on which drug is being investigated. This could e.g. be methods for estimating treatment doses. It is not currently mandatory to report the dose to the RMPS and therefore the dose cannot directly be extracted from the register. It can be argued that the dose can be calculated if the duration of treatment is known, as the redeemed amount of drug is available in the register. However, the duration of treatment is not a variable in the register either. Nevertheless, for some drugs it might be possible to find a reasonable estimate of the dose. This could be possible for drugs used in chronic diseases where the patients are in continuous treatment. In the example with Cymbalta/Xeristar, it was not possible to estimate the dose as the duration of treatment can vary a lot. Another analysis which could be added in some cases is detection of the use of a drug of patients suffering from a contraindicated disease. This is relevant as there may be statements in the SPC about diseases which are contraindicated in treatment with a drug. In some cases it might be possible that redeemed prescriptions

of a certain drug can function as a marker for diseases. This was done in a study by Davidsen and colleagues who used redeemed prescriptions of inhaled beta-2-agonists as a marker for asthma diagnosis.[53]

Besides from applying other methods it could also be relevant to make it mandatory to report additional information to the RMPS. Currently, information on indication and dose of prescribed drugs is sometimes reported to the register, but this is not mandatory and the data on dose and indication is therefore incomplete. It would be an advantage to make it mandatory to report this information. By doing this, off-label use in regard to indication and dose could be readily investigated with a high validity. Furthermore, it would improve the estimate of some of the aspects which were sought estimated in the example of this study.

In summary, an investigation of drug utilization by means of the methods demonstrated in this study offers an additional approach for safety monitoring at the DHMA. Such an investigation can be useful at different stages within safety monitoring, i.e. both identification of potential safety issues and follow-up on initiatives taken by the DHMA. Adding additional methods and additional information to the RMPS constitute initiatives which could possibly enhance and widen the utility of such investigations in safety monitoring.

6 Conclusion

In the present study the utilization of a drug was investigated by means of methods using dispensing data available in the RMPS in order to detect potential safety issues. The investigation was performed on Cymbalta/Xeristar as an example. By means of the applied methods it was possible to investigate the utilization of Cymbalta/Xeristar and detect alarming tendencies in the drug utilization which constituted potential safety issues for the users. It was discussed that an investigation using the methods applied in this study can also be performed for other drugs when adjusted to the drug in question. In regard to this it should be considered that the applied methods have both strengths and limitations and are more applicable for some drugs than others. Overall it was suggested that the methods applied in this study using dispensing data available in the RMPS offer an additional approach with widespread applicability for safety monitoring at the DHMA.

7 Abbreviations

ADR: Adverse drug reaction

ATC: Anatomical Therapeutic Chemical Classification System

DDD: Defined Daily Dosis

DHMA: Danish Health and Medicines Authority

EMA: European Medicines Agency

EPITT: European Pharmacovigilance Issues Tracking Tool

FDA: Food and Drug Administration

PhVWP: Pharmacovigilance Working Party

PSUR: Periodic Safety Update Report

RMPS: Register of Medicinal Products Statistics

SPC: Summary of Product Characteristics

WHO: World Health Organization

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9 Appendices

Appendix A – Example of programs in SAS

Appendix B – Summary of Product Characteristics (SPC) for Cymbalta

Appendix C – Procedural steps taken and scientific information after the authorization of Cymbalta

Appendix A

Example of programs in SAS

Example of programs run in SAS

The following example contains the SAS programs run in this study for estimating the number of users who switch from Cymbalta/Xeristar to another antidepressant. As the programs is only a section of the SAS programs run in this study, some of the shown programs contains references to datasets created in programs not shown in this example. Therefore, the programs in the example cannot be used separately for running the analysis.

Connection to the server is established. Hereafter the virtual library "brugere" containing datasets which will be used in the analysis is assigned. The virtual library "skift" where datasets created during the analysis will be saved is created and assigned.

```
%signon;

libname speciale "\\Lotus\LMS_USERS\ANYJ\brugere";
libname skift "\\Lotus\LMS_USERS\ANYJ\skift";
```

Data on redeemed prescriptions of antidepressants from 2005-2010 are extracted by means of the ATC code.

```
rsubmit;

libname speciale "\\Lotus\LMS_USERS\ANYJ\brugere";
libname skift "\\Lotus\LMS_USERS\ANYJ\skift";


data skift.alantidep01;
           set epikur.epi_kur;
           where aar in ('2005', '2006', '2007', '2008', '2009', '2010')
           and substr(ATC,1,4)='N06A';

run;
endrsubmit;
```

Data on redeemed prescriptions of drugs containing duloxetine as well as the drug bupropion is excluded.

```
rsubmit;

data skift.andreantidep01;
           set skift.alantidep01;
           where ATC^='N06AX21' and ATC^='N06AX12';

run;
endrsubmit;
```

The variable "ALDER" is created.

```
rsubmit;

data skift.andreantidep02;
            set skift.andreantidep01;
            length ALDER $ 5;
            if ALDR <18 then ALDER='<18';
            else if 18<=ALDR<65 then ALDER='18-64';
            else if ALDR >=65 then ALDER='=>65';
            else ALDER='unknown';

run;
endrsubmit;
```

..

The dataset containing data on redeemed prescriptions of Cymbalta/Xeristar, which has been created previously, is sorted by the date of the redeemed prescriptions for each user. Hereafter the data on the last redeemed prescription of each user is retrieved and saved in a dataset.

```
rsubmit;

Proc sort data=speciale.cymxer03 out=skift.cymxer04;
            By kcpr descending eksd;
Run;
endrsubmit;


rsubmit;

Data skift.cymxer05;
            Set skift.cymxer04;
            By kcpr;
            if first.kcpr then output;
Run;
endrsubmit;
```

The dataset containing data on the redeemed prescriptions of antidepressants, except from duloxetine, is sorted by the date of the redeemed prescriptions for each user. Hereafter the data on the first redeemed prescription of each user is retrieved and saved in a dataset.

```
rsubmit;

Proc sort data=skift.andreantidep02 out=skift.andreantidep03;
            By kcpr eksd;
Run;
endrsubmit;


rsubmit;

Data skift.andreantidep04;
            Set skift.andreantidep03;
            By kcpr;
            if first.kcpr then output;
Run;
endrsubmit;
```

The users who have redeemed another antidepressant <90 days after their last redemption of Cymbalta/Xeristar are identified.

```
rsubmit;

Proc sql;
Create table skift.cymxertilandre90_01 (where=(0 < (mindatob-maxdatoa) <
90)) as
Select a.kcpr, b.koen, b.alder, b.aar, b.ATC,
           (a.eksd) as maxdatoa format YYMMDD6.,
           (b.eksd) as mindatob format YYMMDD6.
From  skift.cymxer05 a, skift.andreantidep04 b
Where a.kcpr=b.kcpr
Group by a.kcpr;

Quit;
endrsubmit;
```

The number of users who switch per year is calculated and saved in a dataset.

```
rsubmit;

proc sql;
create table skift.cymxertilandre90_02 as
select aar, koen, alder, count(kcpr) as antal
from skift.cymxertilandre90_01
group by aar, koen, alder;

quit;
endrsubmit;
```

The dataset is exported to Excel. Hereafter the connection to the server is ended.

```
rsubmit;

proc export data=skift.cymxertilandre90_02
                    dbms=excel2002
          outfile="\\Lotus\lms_users\ANYJ\Resultater\cymxertilandre90_02.x
ls";
run;
endrsubmit;

%signoff;
```

Appendix B

Summary of Product Characteristics (SPC) for Cymbalta

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 30 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg of duloxetine (as hydrochloride).

Excipients:
Each capsule contains 8.6 mg sucrose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.
Opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Cymbalta is indicated in adults.
For further information see section 5.1.

4.2 Posology and method of administration

Posology
Major depressive disorder
The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.

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

After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised anxiety disorder
The recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.

In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above).

Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or

120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.

After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Diabetic peripheral neuropathic pain
The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see section 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

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

The therapeutic benefit should be reassessed regularly (at least every three months) (see section 5.1).

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with Cymbalta 120 mg per day for major depressive disorder, for which data are limited (see sections 4.4 and 5.2).

Children and adolescents
Duloxetine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see section 4.4).

Hepatic impairment
Cymbalta must not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Cymbalta must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Discontinuation of treatment
Abrupt discontinuation should be avoided. When stopping treatment with Cymbalta the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration
For oral use.

4.3 Contraindications

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

Concomitant use of Cymbalta with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

Cymbalta should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with Cymbalta is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and seizures
Cymbalta should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing Cymbalta to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

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

St John's wort
Adverse reactions may be more common during concomitant use of Cymbalta and herbal preparations containing St John's wort (Hypericum perforatum).

Suicide
Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Cymbalta is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients and in particular those at high risk should accompany medicinal product therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. Cymbalta should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia
Hyponatraemia has been reported when administering Cymbalta, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo. The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2

weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Elderly
Data on the use of Cymbalta 120mg in elderly patients with major depressive disorders are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2). Data on the use of Cymbalta in elderly patients with generalised anxiety disorder are limited.

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

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Sucrose
Cymbalta hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with nonselective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of Cymbalta with selective, reversible MAOIs is not recommended (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{o-t} 6-fold. Therefore Cymbalta should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

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

Serotonin syndrome: In rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g.

paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if Cymbalta is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

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

Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if Cymbalta is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

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

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

Effects of other medicinal products on duloxetine
Antacids and H_2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids or duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

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

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3).

The potential risk for humans is unknown.

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

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of

cases have occurred either at birth or within a few days of birth.

Cymbalta should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of Cymbalta while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Cymbalta may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

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

b. Tabulated summary of adverse reactions
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7819 patients, 4823 on duloxetine and 2996 on placebo) in depression, generalised anxiety disorder and diabetic neuropathic pain.

Table 1: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare
Infections and Infestations				
		Laryngitis		
Immune System Disorders				
			Anaphylactic reaction Hyper-sensitivity disorder	
Endocrine Disorders				
			Hypo-thyroidism	
Metabolism and Nutrition Disorders				
	Decreased Appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH[6]	
Psychiatric Disorders				
	Insomnia Agitation Libido decreased	Suicidal ideation[5,7] Sleep disorder	Suicidal behaviour[5,7] Mania	

Very common	Common	Uncommon	Rare	Very Rare
	Anxiety Orgasm abnormal Abnormal dreams	Bruxism Disorientation Apathy	Hallucinations Aggression and anger[4]	
Nervous System Disorders				
Headache (14.4%) Somnolence (10.4%)	Dizziness Lethargy Tremor Paraesthesia	Myoclonus Akathisia[7] Nervousness Disturbance in attention Dysgeusia Dyskinesia Restless legs syndrome Poor quality sleep	Serotonin syndrome[6] Convulsion[1] Psychomotor restlessness[6] Extra-pyramidal symptoms[6]	
Eye Disorders				
	Blurred vision	Mydriasis Visual impairment	Glaucoma	
Ear and Labyrinth Disorders				
	Tinnitus[1]	Vertigo Ear pain		
Cardiac Disorders				
	Palpitations	Tachycardia Supra-ventricular arrhythmia, mainly atrial fibrillation		
Vascular Disorders				
	Blood pressure increase[3] Flushing	Syncope[2] Hypertension[3,7] Orthostatic hypotension[2] Peripheral coldness	Hypertensive crisis[3,6]	
Respiratory, Thoracic and Mediastinal Disorders				
	Yawning	Throat tightness Epistaxis		
Gastrointestinal Disorders				
Nausea (24.1%) Dry mouth (13.1%)	Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage[7] Gastroenteritis Eructation Gastritis	Stomatitis Haematochezia Breath odour	
Hepato-biliary Disorders				
		Hepatitis[3] Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure[6] Jaundice[6]	
Skin and Subcutaneous Tissue Disorders				
	Sweating increased Rash	Night sweats Urticaria Dermatitis contact	Stevens-Johnson Syndrome[6] Angio-neurotic	

Very common	Common	Uncommon	Rare	Very Rare
		Cold sweat Photo-sensitivity reactions Increased tendency to bruise	oedema[6]	
Musculoskeletal and Connective Tissue Disorders				
	Musculo-skeletal pain Muscle spasm	Muscle tightness Muscle twitching	Trismus	
Renal and Urinary Disorders				
	Dysuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal	
Reproductive System and Breast Disorders				
	Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction	Menopausal symptoms Galactorrhoea Hyperprolactinaemia	
General Disorders and Administration Site Conditions				
	Fatigue	Chest pain[7] Falls[8] Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance		
Investigations				
	Weight decrease	Weight increase Blood creatine phosphokinase increased Blood potassium increased	Blood cholesterol increased	

[1] Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.
[2] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
[3] See section 4.4.
[4] Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.
[5] Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).
[6] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.
[7] Not statistically significantly different from placebo.
[8] Falls were more common in the elderly (≥65 years old)

c. Description of selected adverse reactions

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

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

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action
Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Pharmacodynamic effects
Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Clinical efficacy and safety
Major Depressive Disorder: Cymbalta was studied in a clinical programme involving 3,158 patients (1,285 patient-years of exposure) meeting DSM-IV criteria for major depression. The efficacy of Cymbalta at the recommended dose of 60 mg once a day was demonstrated in three out of three randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder. Overall, Cymbalta's efficacy has been demonstrated at daily doses between 60 and 120 mg in a total of five out of seven randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder.

Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression). Response and remission rates were also statistically significantly higher with Cymbalta compared with placebo. Only a small proportion of patients included in pivotal clinical trials had severe depression (baseline HAM-D>25).

In a relapse prevention study, patients responding to 12-weeks of acute treatment with open-label Cymbalta 60 mg once daily were randomised to either Cymbalta 60 mg once daily or placebo for a further 6-months. Cymbalta 60 mg once daily demonstrated a statistically significant superiority compared to placebo ($p=0.004$) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 17% and 29% for duloxetine and placebo, respectively.

During 52 weeks of placebo-controlled double blind treatment, duloxetine-treated patients with recurrent MDD had a significantly longer symptom free period ($p<0.001$) compared with patients randomised to placebo. All patients had previously responded to duloxetine during open-label duloxetine treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled double blind treatment phase 14.4% of the duloxetine-treated patients and 33.1% of the placebo-treated patients experience a return of their depressive symptoms ($p<0.001$).

The effect of Cymbalta 60 mg once a day in elderly depressed patients (≥65 years) was specifically examined in a study that showed a statistically significative difference in the reduction of the HAMD17 score for duloxetine-treated patients compared to placebo. Tolerability of Cymbalta 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120mg per day) are limited and thus, caution is recommended when treating this population.

Generalised Anxiety Disorder: Cymbalta demonstrated statistically significant superiority over placebo in five out of five studies including four randomised, double-blind, placebo-controlled acute studies and a relapse prevention study in adult patients with generalised anxiety disorder.

Cymbalta demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. Response and remission rates were also higher with Cymbalta compared to placebo. Cymbalta showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In a relapse prevention study, patients responding to 6 months of acute treatment with open-label Cymbalta were randomised to either Cymbalta or placebo for a further 6-months. Cymbalta 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo ($p<0.001$) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for Cymbalta and 42% for placebo.

Diabetic Peripheral Neuropathic Pain: The efficacy of Cymbalta as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary

outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, Cymbalta 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% of patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

In an open label long-term uncontrolled study, the pain reduction in patients responding to 8-weeks of acute treatment of Cymbalta 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Cymbalta in all subsets of the paediatric population in the treatment of major depressive disorder, diabetic neuropathic pain and generalised anxiety disorder. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations
Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of

clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breast-feeding mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose
Hypromellose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate

Capsule shell:
30 mg:
Gelatin
Sodium lauryl sulfate
Titanium dioxide (E171)
Indigo carmine (E132)
Edible green ink

Edible green ink contains:
Black iron oxide - synthetic (E172)
Yellow iron oxide - synthetic (E172)
Propylene glycol
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30º C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), polyethylene (PE), and polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminium foil.

Cymbalta 30 mg is available in packs of 7, 28 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/296/001
EU/1/04/296/006
EU/1/04/296/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2004
Date of latest renewal: 24 June 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 60 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 60 mg of duloxetine (as hydrochloride).

Excipients:
Each capsule contains 17.2 mg sucrose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.
Opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Cymbalta is indicated in adults.
For further information see section 5.1.

4.2 Posology and method of administration

Posology
Major depressive disorder
The starting and recommended maintenance dose is 60 mg once daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day have been evaluated from a safety perspective in clinical trials. However, there is no clinical evidence suggesting that patients not responding to the initial recommended dose may benefit from dose up-titrations.

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

After consolidation of the antidepressive response, it is recommended to continue treatment for several months, in order to avoid relapse. In patients responding to duloxetine, and with a history of repeated episodes of major depression, further long-term treatment at a dose of 60 to 120 mg/day could be considered.

Generalised anxiety disorder
The recommended starting dose in patients with generalised anxiety disorder is 30 mg once daily with or without food. In patients with insufficient response the dose should be increased to 60 mg, which is the usual maintenance dose in most patients.

In patients with co-morbid major depressive disorder, the starting and maintenance dose is 60 mg once daily (please see also dosing recommendation above).

Doses up to 120 mg per day have been shown to be efficacious and have been evaluated from a safety perspective in clinical trials. In patients with insufficient response to 60 mg, escalation up to 90 mg or

120 mg may therefore be considered. Dose escalation should be based upon clinical response and tolerability.

After consolidation of the response, it is recommended to continue treatment for several months, in order to avoid relapse.

Diabetic peripheral neuropathic pain
The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see section 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

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

The therapeutic benefit should be reassessed regularly (at least every three months) (see section 5.1).

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly, especially with Cymbalta 120 mg per day for major depressive disorder, for which data are limited (see sections 4.4 and 5.2).

Children and adolescents
Duloxetine is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see section 4.4).

Hepatic impairment
Cymbalta must not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Cymbalta must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Discontinuation of treatment
Abrupt discontinuation should be avoided. When stopping treatment with Cymbalta the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration
For oral use.

4.3 Contraindications

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

Concomitant use of Cymbalta with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

Cymbalta should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with Cymbalta is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and seizures
Cymbalta should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing Cymbalta to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

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

St John's wort
Adverse reactions may be more common during concomitant use of Cymbalta and herbal preparations containing St John's wort (Hypericum perforatum).

Suicide
Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Cymbalta is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients and in particular those at high risk should accompany medicinal product therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Diabetic Peripheral Neuropathic Pain: As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. Cymbalta should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia
Hyponatraemia has been reported when administering Cymbalta, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo. The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2

weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Elderly
Data on the use of Cymbalta 120mg in elderly patients with major depressive disorders are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2). Data on the use of Cymbalta in elderly patients with generalised anxiety disorder are limited.

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

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including *s*evere elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Sucrose
Cymbalta hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with nonselective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of Cymbalta with selective, reversible MAOIs is not recommended (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{o-t} 6-fold. Therefore Cymbalta should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

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

Serotonin syndrome: In rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g.

paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if Cymbalta is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

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

Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if Cymbalta is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

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

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

Effects of other medicinal products on duloxetine
Antacids and H_2 antagonists: Co-administration of duloxetine with aluminium- and magnesium-containing antacids or duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

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

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3).

The potential risk for humans is unknown.

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

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include

hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Cymbalta should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of Cymbalta while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Cymbalta may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

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

b. Tabulated summary of adverse reactions
Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7819 patients, 4823 on duloxetine and 2996 on placebo) in depression, generalised anxiety disorder and diabetic neuropathic pain.

Table 1: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare
Infections and Infestations				
		Laryngitis		
Immune System Disorders				
			Anaphylactic reaction Hyper-sensitivity disorder	
Endocrine Disorders				
			Hypo-thyroidism	
Metabolism and Nutrition Disorders				
	Decreased Appetite	Hyperglycaemia (reported especially in diabetic patients)	Dehydration Hyponatraemia SIADH[6]	
Psychiatric Disorders				
	Insomnia Agitation	Suicidal ideation[5,7]	Suicidal behaviour[5,7]	

Very common	Common	Uncommon	Rare	Very Rare
	Libido decreased Anxiety Orgasm abnormal Abnormal dreams	Sleep disorder Bruxism Disorientation Apathy	Mania Hallucinations Aggression and anger[4]	
Nervous System Disorders				
Headache (14.4%) Somnolence (10.4%)	Dizziness Lethargy Tremor Paraesthesia	Myoclonus Akathisia[7] Nervousness Disturbance in attention Dysgeusia Dyskinesia Restless legs syndrome Poor quality sleep	Serotonin syndrome[6] Convulsion[1] Psychomotor restlessness[6] Extra-pyramidal symptoms[6]	
Eye Disorders				
	Blurred vision	Mydriasis Visual impairment	Glaucoma	
Ear and Labyrinth Disorders				
	Tinnitus[1]	Vertigo Ear pain		
Cardiac Disorders				
	Palpitations	Tachycardia Supra-ventricular arrhythmia, mainly atrial fibrillation		
Vascular Disorders				
	Blood pressure increase[3] Flushing	Syncope[2] Hypertension[3,7] Orthostatic hypotension[2] Peripheral coldness	Hypertensive crisis[3,6]	
Respiratory, Thoracic and Mediastinal Disorders				
	Yawning	Throat tightness Epistaxis		
Gastrointestinal Disorders				
Nausea (24.1%) Dry mouth (13.1%)	Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage[7] Gastroenteritis Eructation Gastritis	Stomatitis Haematochezia Breath odour	
Hepato-biliary Disorders				
		Hepatitis[3] Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure[6] Jaundice[6]	
Skin and Subcutaneous Tissue Disorders				
	Sweating increased	Night sweats Urticaria	Stevens-Johnson Syndrome[6]	

Very common	Common	Uncommon	Rare	Very Rare
	Rash	Dermatitis contact Cold sweat Photo-sensitivity reactions Increased tendency to bruise	Angio-neurotic oedema[6]	
Musculoskeletal and Connective Tissue Disorders				
	Musculo-skeletal pain Muscle spasm	Muscle tightness Muscle twitching	Trismus	
Renal and Urinary Disorders				
	Dysuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased	Urine odour abnormal	
Reproductive System and Breast Disorders				
	Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction	Menopausal symptoms Galactorrhoea Hyperprolactinaemia	
General Disorders and Administration Site Conditions				
	Fatigue	Chest pain[7] Falls[8] Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance		
Investigations				
	Weight decrease	Weight increase Blood creatine phosphokinase increased Blood potassium increased	Blood cholesterol increased	

[1] Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.
[2] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
[3] See section 4.4.
[4] Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.
[5] Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).
[6] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.
[7] Not statistically significantly different from placebo.
[8] Falls were more common in the elderly (≥65 years old)

c. Description of selected adverse reactions
Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

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

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action
Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Pharmacodynamic effects
Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of

duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Clinical efficacy and safety
Major Depressive Disorder: Cymbalta was studied in a clinical programme involving 3,158 patients (1,285 patient-years of exposure) meeting DSM-IV criteria for major depression. The efficacy of Cymbalta at the recommended dose of 60 mg once a day was demonstrated in three out of three randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder. Overall, Cymbalta's efficacy has been demonstrated at daily doses between 60 and 120 mg in a total of five out of seven randomised, double-blind, placebo-controlled, fixed dose acute studies in adult outpatients with major depressive disorder.

Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression). Response and remission rates were also statistically significantly higher with Cymbalta compared with placebo. Only a small proportion of patients included in pivotal clinical trials had severe depression (baseline HAM-D>25).

In a relapse prevention study, patients responding to 12-weeks of acute treatment with open-label Cymbalta 60 mg once daily were randomised to either Cymbalta 60 mg once daily or placebo for a further 6-months. Cymbalta 60 mg once daily demonstrated a statistically significant superiority compared to placebo (p=0.004) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 17% and 29% for duloxetine and placebo, respectively.

During 52 weeks of placebo-controlled double blind treatment, duloxetine-treated patients with recurrent MDD had a significantly longer symptom free period (p<0.001) compared with patients randomised to placebo. All patients had previously responded to duloxetine during open-label duloxetine treatment (28 to 34 weeks) at a dose of 60 to 120 mg/day. During the 52-week placebo-controlled double blind treatment phase 14.4% of the duloxetine-treated patients and 33.1% of the placebo-treated patients experience a return of their depressive symptoms (p<0.001).

The effect of Cymbalta 60 mg once a day in elderly depressed patients (≥65 years) was specifically examined in a study that showed a statistically significative difference in the reduction of the HAMD17 score for duloxetine-treated patients compared to placebo. Tolerability of Cymbalta 60 mg once daily in elderly patients was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120mg per day) are limited and thus, caution is recommended when treating this population.

Generalised Anxiety Disorder: Cymbalta demonstrated statistically significant superiority over placebo in five out of five studies including four randomised, double-blind, placebo-controlled acute studies and a relapse prevention study in adult patients with generalised anxiety disorder.

Cymbalta demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. Response and remission rates were also higher with Cymbalta compared to placebo. Cymbalta showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In a relapse prevention study, patients responding to 6 months of acute treatment with open-label Cymbalta were randomised to either Cymbalta or placebo for a further 6-months. Cymbalta 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo (p<0.001) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for Cymbalta and 42% for placebo.

Diabetic Peripheral Neuropathic Pain: The efficacy of Cymbalta as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed

dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, Cymbalta 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% of patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

In an open label long-term uncontrolled study, the pain reduction in patients responding to 8-weeks of acute treatment of Cymbalta 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Cymbalta in all subsets of the paediatric population in the treatment of major depressive disorder, diabetic neuropathic pain and generalised anxiety disorder. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations
Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breast-feeding mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose
Hypromellose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)

Triethyl citrate

Capsule shell:
60 mg:
Gelatin
Sodium lauryl sulfate
Titanium dioxide (E171)
Indigo carmine (E132)
Yellow iron oxide (E172)
Edible white ink

Edible white ink contains:
Titanium dioxide (E171)
Propylene glycol
Shellac
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30º C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), polyethylene (PE), and polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminium foil.

Cymbalta 60 mg is available in packs of 28, 56, 84, 98, 100 (Each pack contains 5 cartons of 20 capsules) and 500 capsules (Each pack contains 25 cartons of 20 capsules).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/296/002
EU/1/04/296/003
EU/1/04/296/004
EU/1/04/296/005
EU/1/04/296/007
EU/1/04/296/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2004
Date of latest renewal: 24 June 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Lilly S.A.
Avda. de la Industria Nº 30,
28108 Alcobendas
Madrid
Spain

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 05 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs
PSURs will have to be submitted with a 1-year frequency, until otherwise specified by the CHMP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 30 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 30 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 30 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard gastro-resistant capsules
28 hard gastro-resistant capsules
98 hard gastro-resistant capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/296/001
EU/1/04/296/006
EU/1/04/296/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cymbalta 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
30 mg hard gastro-resistant capsules

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 30 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 60 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 60 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 60 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28, hard gastro-resistant capsules
84, hard gastro-resistant capsules
98, hard gastro-resistant capsules
56, hard gastro-resistant capsules
500, hard gastro-resistant capsules (25 cartons of 20 capsules).
100, hard gastro-resistant capsules (5 cartons of 20 capsules)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/296/002 (28 capsules)
EU/1/04/296/003 (84 capsules)
EU/1/04/296/004 (98 capsules)
EU/1/04/296/005 (56 capsules)
EU/1/04/296/007 (500 capsules)
EU/1/04/296/008 (100 capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cymbalta 60 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
60 mg hard gastro-resistant capsules

1. NAME OF THE MEDICINAL PRODUCT

Cymbalta 60 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cymbalta 30 mg hard gastro-resistant capsules
Cymbalta 60 mg hard gastro-resistant capsules
Duloxetine (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CYMBALTA IS AND WHAT IT IS USED FOR

Cymbalta increases the levels of serotonin and noradrenaline in the nervous system.

Cymbalta is used in adults to treat:
- depression
- generalised anxiety disorder (chronic feeling of anxiety or nervousness)
- diabetic neuropathic pain (often described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain)

Your doctor may continue to give you Cymbalta when you are feeling better to prevent your depression or anxiety from returning.

2. BEFORE YOU TAKE CYMBALTA

DO NOT take Cymbalta if you:
- are allergic (hypersensitive) to duloxetine or any of the other ingredients of Cymbalta (see 'Further Information')
- have liver disease
- have severe kidney disease
- are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor (MAOI) (see 'Taking other medicines')
- are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacin which are used to treat some infections
- are taking other medicines containing duloxetine (see 'Taking other medicines')

Talk to your doctor if you have high blood pressure or heart disease. Your doctor will tell you if you should be taking Cymbalta.

Take special care with Cymbalta
The following are reasons why Cymbalta may not be suitable for you. Talk to your doctor before you take the medicine if you:

- are taking other medicines to treat depression (see 'Taking other medicines')
- are taking St. John's Wort, a herbal treatment (*Hypericum perforatum*)
- have kidney disease
- have had seizures (fits)
- have had mania
- suffer from bipolar disorder
- have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- have a history of bleeding disorders (tendency to develop bruises)
- are at risk of low sodium levels (for example if you are taking diuretics, especially if you are elderly)
- are currently being treated with another medicine which may cause liver damage
- are taking other medicines containing duloxetine (see 'Taking other medicines')

Cymbalta may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

Thoughts of suicide and worsening of your depression or anxiety disorder
If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this if you:
- have previously had thoughts about killing or harming yourself
- are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Use in children and adolescents under 18 years of age
Cymbalta should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Cymbalta for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Cymbalta for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Cymbalta. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of Cymbalta in this age group have not yet been demonstrated.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The main ingredient of Cymbalta, duloxetine, is used in other medicines for other conditions:
- diabetic neuropathic pain, depression, anxiety and urinary incontinence

Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take Cymbalta with other medicines. **Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.**

You should also tell your doctor if you are taking any of the following:

Monoamine oxidase inhibitors (MAOIs): You should not take Cymbalta if you are taking, or have recently taken (within the last 14 days) another antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Taking a MAOI together with many prescription medicines, including Cymbalta, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take Cymbalta. Also, you need to wait at least 5 days after you stop taking Cymbalta before you take a MAOI.

Medicines that cause sleepiness: These include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbital and antihistamines.

Medicines that increase the level of serotonin: Triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Cymbalta, you should see your doctor.

***Oral anticoagulants or antiplatelet agents*:** Medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding.

Taking Cymbalta with food and drink
Cymbalta may be taken with or without food. Care should be taken if you drink alcohol while you are being treated with Cymbalta.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

- Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking Cymbalta. You should use Cymbalta only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

  Make sure your midwife and/or doctor knows you are on Cymbalta. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

  If you take Cymbalta near the end of your pregnancy, your baby might have some symptoms when it is born. These usually begin at birth or within a few days of your baby being born. These symptoms may include floppy muscles, trembling, jitteriness, not feeding properly, trouble with breathing and fits. If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, contact your doctor or midwife who will be able to advise you.

- Tell your doctor if you are breast-feeding. The use of Cymbalta while breastfeeding is not recommended. You should ask your doctor or pharmacist for advice.

Driving and using machines
Cymbalta may make you feel sleepy or dizzy. Do not drive or use any tools or machines until you know how Cymbalta affects you.

Important information about some of the ingredients of Cymbalta
Cymbalta contains **sucrose.** If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CYMBALTA

Always take Cymbalta exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Cymbalta is for oral use. You should swallow your capsule whole with a drink of water.

Cymbalta starts to work in most people with depression or anxiety within two weeks of starting treatment.

Cymbalta starts to work in most people with diabetic neuropathic pain within 1 week of starting treatment.

For depression and diabetic neuropathic pain:
The usual dose of Cymbalta is 60 mg once a day, but your doctor will prescribe the dose that is right for you.

For generalised anxiety disorder:
The usual starting dose of Cymbalta is 30 mg once a day after which most patients will receive 60 mg once a day, but your doctor will prescribe the dose that is right for you. The dose may be adjusted up to 120 mg a day based on your response to Cymbalta.

To help you remember to take Cymbalta, you may find it easier to take it at the same times every day.

Talk with your doctor about how long you should keep taking Cymbalta. Do not stop taking Cymbalta without talking to your doctor.

If you take more Cymbalta than you should
Call your doctor or pharmacist immediately if you take more than the amount of Cymbalta prescribed by your doctor. Symptoms of overdose include sleepiness, coma, serotonin syndrome (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits, vomiting and fast heart rate.

If you forget to take Cymbalta
If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take a double dose to make up for a forgotten dose. Do not take more than the daily amount of Cymbalta that has been prescribed for you in one day.

If you stop taking Cymbalta
DO NOT stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need Cymbalta he or she will ask you to reduce your dose over at least 2 weeks before stopping treatment altogether.

Some patients who stop taking Cymbalta suddenly have had symptoms such as:
- dizziness, tingling feelings like pins and needles, sleep disturbances (vivid dreams, nightmares, inability to sleep), fatigue, sleepiness, feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), shaking (tremor), headaches, feeling irritable, diarrhoea, excessive sweating or vertigo.

These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

If you have further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cymbalta can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a few weeks.

Very common side effects (affects more than 1 user in 10)
- headache, feeling sleepy
- feeling sick (nausea), dry mouth

Common side effects (affects 1 to 10 users in 100)
- lack of appetite
- trouble sleeping, feeling agitated, less sex drive, anxiety, difficulty or failure to experience orgasm, unusual dreams
- dizziness, feeling sluggish, tremor, numbness, including numbness, pricking or tingling of the skin
- blurred eyesight
- tinnitus (hearing sound in the ear when there is no external sound)
- feeling the heart pumping in the chest,
- increased blood pressure, flushing
- increased yawning
- constipation, diarrhoea, stomach pain, being sick (vomiting), heartburn or indigestion, breaking wind
- increased sweating, (itchy) rash
- muscle pain, muscle spasm
- painful urination,
- problems getting an erection, changes in ejaculation
- fatigue
- weight loss

Uncommon side effects (affects 1 to 10 users in 1,000)
- throat inflammation that causes a hoarse voice
- suicidal thoughts, difficulty sleeping, grinding or clenching the teeth, feeling disorientated, lack of motivation
- sudden involuntary jerks or twitches of the muscles, sensation of restlessness or an inability to sit or stand still, feeling nervous, difficulty concentrating, changes in sense of taste, difficulty controlling movement e.g. lack of coordination or involuntary movements of the muscles, restless legs syndrome, poor sleep quality
- large pupils (the dark centre of the eye), problems with eyesight
- feeling of dizziness or “spinning” (vertigo), ear pain
- fast and/or irregular heart beat
- fainting, dizziness, lightheadedness or fainting on standing up, cold fingers and/or toes
- throat tightness, nose bleeds
- vomiting blood, or black tarry stools (faeces), gastroenteritis, burping
- inflammation of the liver that may cause abdominal pain and yellowing of the skin or whites of the eyes
- night sweats, hives, cold sweats, sensitivity to sunlight, increased tendency to bruise
- muscle tightness, muscle twitching
- difficulty or inability to pass urine, difficulty to start urinating, needing to pass urine during the night, needing to pass more urine than normal, having a decreased urine flow
- abnormal vaginal bleeding, abnormal periods, including heavy, painful, irregular or prolonged periods, unusually light or missed periods,
- chest pain, falls (mostly in elderly people), feeling cold, thirst, shivering, feeling hot, abnormal gait
- weight gain

- Cymbalta may cause effects that you may not be aware of, such as increases in liver enzymes or blood levels of potassium, creatine phosphokinase, sugar, or cholesterol

Rare side effects (affects 1 to 10 users in 10,000)
- serious allergic reaction which causes difficulty in breathing or dizziness with swollen tongue or lips, allergic reactions
- decreased thyroid gland activity which can cause tiredness or weight gain
- dehydration, low levels of sodium in the blood (mostly in elderly people; the symptoms may include feeling dizzy, weak, confused, sleepy or very tired, or feeling or being sick, more serious symptoms are fainting, fits or falls), syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)
- suicidal behaviour, mania (over activity, racing thoughts and decreased need for sleep), hallucinations, aggression and anger
- "Serotonin syndrome" (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits
- increased pressure in the eye (glaucoma)
- inflammation of the mouth, passing bright red blood in your stools, bad breath
- liver failure, yellowing of the skin or whites of the eyes (jaundice)
- Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals), serious allergic reaction which causes swelling of the face or throat (angioedema)
- contraction of the jaw muscle
- abnormal urine odour
- menopausal symptoms, abnormal production of breast milk in men or women

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CYMBALTA

Keep out of the reach and sight of children.

Do not use Cymbalta after the expiry date which is stated on the carton.

Store in the original package to protect from moisture. Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cymbalta contains
The **active** substance is duloxetine.
Each capsule contains 30 or 60 mg of duloxetine (as hydrochloride).

The **other** ingredients are:
Capsule content: hypromellose, hypromellose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate *(See end of section 2 for further information on sucrose).*
Capsule shell: gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), yellow iron oxide (E172) (60 mg only) and edible green ink (30 mg) or edible white ink (60 mg).
Edible green ink: synthetic black iron oxide (E172), synthetic yellow iron oxide (E172), propylene glycol, shellac.
Edible white ink: titanium dioxide (E171), propylene glycol, shellac, povidone.

What Cymbalta looks like and contents of the pack
Cymbalta is a hard gastro-resistant capsule. Each capsule of Cymbalta contains pellets of duloxetine hydrochloride with a covering to protect them from stomach acid.

Cymbalta is available in 2 strengths: 30 mg and 60 mg.
The 30 mg capsules are blue and white and are printed with '30 mg' and the code '9543'.
The 60 mg capsules are blue and green and are printed with '60 mg' and the code '9542'.

Cymbalta 30 mg is available in packs of 7, 28 and 98 capsules.
Cymbalta 60 mg is available in packs of 28, 56, 84, 98, 100 and 500 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.
Manufacturer: Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Appendix C

Procedural steps taken and scientific information after the authorization of Cymbalta

Cymbalta

Procedural steps taken and scientific information after the authorisation

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
WS/0135	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. - Update of the SmPC section 4.4 to include NSAIDS and ASA as examples of antiplatelet agents. - Update of the SmPC section 4.8 to include terms 'menstrual disorder', 'blood potassium increased', 'dry eye' and 'falls' to the tabulated summary of adverse reactions and to add 'somnolence' to the list of most commonly reported withdrawal symptoms. A footnote "falls were more common in the elderly (more than 65 years old)" was added to 'falls'. Additionally frequencies of some currently listed ADRs were changed. These updates were based on the most recent CCDS from February 2011. The Package Leaflet has been updated accordingly. Furthermore, minor editorial	23/06/2011	26/07/2011	SPC, PL	In this variation sections of the product information which provide information on precautions one should take before taking duloxetines were updated with examples of medicines that prevent the blood from clotting, e.g. non steroidal anti-inflammatory drugs and acetylsalicylic acid. New information was also added to the sections of the product information describing possible side effects, for example: menstrual disorder, increase in blood potassium levels, dry eye and falls. Somnolence was added to the list of most commonly reported withdrawal symptoms. It was also mentioned that the patients older than 65 years might experience falls more often. In addition, frequencies of several side effects were updated.

[1] Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.
[2] No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.
[3] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	changes were also introduced to the product information. C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IA/0048/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS, C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	28/02/2011	n/a		
WS/0071	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	27/01/2011	SPC, Annex II, Labelling, PL	This variation updates the SmPC section 4.4 with the laboratory measure of the seriousness of low sodium levels in blood and underlines the fact that the elderly are at risk of low sodium levels. The Package Leaflet has been updated accordingly. Additionally, the contact details for the local representatives in Estonia for the Ariclaim, Cymbalta, Xeristar and Yentreve Package Leaflets have been updated.
IG/0031	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the active substance, starting material, reagent or intermediate used in	17/12/2010	n/a		

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	the manufacture of the active substance				
WS/0011/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation, C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	22/07/2010	06/09/2010	SPC, PL	This application was submitted for a group of variations consisting of two type 1B variations. In the variation C.I.z the MAH updated the section 4.6 'Pregnancy and lactation' of the SmPC with symptoms and time to onset of neonatal drug withdrawal syndrome and added galactorrhoea and hyperprolactinaemia to section 4.8 'Undesirable effects' of the SmPC as the result of the assessment of PSUR-9. The Package Leaflet has been updated accordingly. In the variation C.I.3.a the MAH updated the section 'Pregnancy and lactation' of the Product Information following the class review for SSRIs/SNRIs to inform that when taken during pregnancy SSRI/SNRIs may increase the risk of persistent pulmonary hypertension in neonates. In addition the MAH introduced minor administrative, editorial and linguistic changes to the Product Information.
IA/0047	To submit new, updated and unchanged TSE Ph. Eur. certificates of suitability for the gelatine used by the current authorised manufacturer of the capsules and for an alternative new suppplier. 22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	24/11/2009	n/a		
IB/0046	35_b_Change in weight of coating/capsule shells - gastro-res., modif., prol. release ph. forms	24/11/2009	n/a		
II/0036	Extension of indication to include treatment of major depressive disorder. Extension of Indication	22/10/2009	20/11/2009	SPC	The CHMP assessment report will be published after deletion of confidential information.
IB/0045	34_b_01_Change in colour/flavour - Increase or addition: colouring system	13/11/2009	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/07/2009	n/a	PL	
II/0041	Update of section 4.5 of the Summary of	29/05/2009	01/07/2009	SPC	Study F1J-MC-HMFP was an open-label study with the primary

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	Product Characteristics to reflect the results of a recent duloxetine/warfarin interaction study (study F1J-MC-HMFP). Furthermore, the term "adolescents" was included in section 4.2 of the SPC in order to align this section with the current QRD template. Update of Summary of Product Characteristics				objective to evaluate the anticoagulant effects of multiple doses of warfarin when taken at the same time with multiple doses of duloxetine as measured by changes in the international normalized ratio (INR). Increases in INR values were reported when duloxetine was co-administered with warfarin. However, concomitant administration of duloxetine with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of warfarin.
R/0038	Renewal of Marketing Authorisation.	23/04/2009	24/06/2009	SPC, Annex II, Labelling, PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Cymbalta continues to be favurable. The MAH will continue to submit a yearly PSUR.
II/0040	to change the finished product specification. Quality changes	23/04/2009	28/04/2009		
IB/0042	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	27/04/2009	n/a		
IA/0043	32_b_Change in batch size of the finished product - downscaling down to 10-fold	02/04/2009	n/a		
II/0037	Update of Sections 4.8 “Undesirable effects” and 4.9 “Overdose” of the Summary of Product Characteristics (SPC) to reflect the most recent clinical trial data findings of the 7th PSUR. The Package Leaftlet (PL) was updated accordingly. In addition, this variation implements the outcome of a recent user testing of the PL of duloxetine-containing products.	19/02/2009	25/03/2009	SPC, PL	A new data lock point for all placebo-controlled clinical studies resulted in a significant increase in the size of the overall database and thus a more robust basis for the determination of Adverse Drug Reactions (ADRs). As a consequence, the frequency of some ADRs was updated in the SPC. Regarding spontaneous data, the MAH identified one new ADR (“restless legs syndrome”) as well as new information on overdose in the most recent PSUR (PSUR 7) submitted in September 2008, and updated the SPC accordingly.

No	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
	Update of Summary of Product Characteristics and Package Leaflet				Finally, the MAH has undertaken a user testing of the PL of duloxetine-containing products in 2008 and the results of these were implemented in the PL.
II/0035	Update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) to reflect new data from a clinical study that investigated the maintenance of effect of duloxetine over 6 months of treatment. The opportunity is also taken to correct some minor typos in the SPC, Labelling and Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/01/2009	02/03/2009	SPC, Labelling, PL	Study 'HMEM' was designed to investigate the maintenance of effect of duloxetine 60 mg once daily in patients with Diabetic Peripheral Neuropathic Pain (DPNP) who responded to an initial 8 weeks of therapy. This variation application was submitted in order to update the SPC to reflect the results of study HMEM. The study demonstrated that, for patients who showed an initial response to DPNP therapy with duloxetine, the pain relief observed with duloxetine 60 mg is maintained over a 6-month period. The variation resulted in the following SPC wording: Section 4.2: [Diabetic Peripheral Neuropathic Pain Response to treatment should be evaluated after 2 months. In patients with inadequate initial response, additional response after this time is unlikely…] Section 5.1 […In an open label long-term uncontrolled study, the pain reduction in patients responding to 8-weeks of acute treatment of CYMBALTA 60 mg once daily was maintained for a further 6-months as measured by change on the Brief Pain Inventory (BPI) 24-hour average pain item…]
IA/0039	38_a_Change in test procedure of finished product - minor change to approved test procedure	24/02/2009	n/a		
IB/0033	13_b_Change in test proc. for active substance - other changes (replacement/addition)	31/07/2008	n/a		
II/0027	Extension of indication for Cymbalta to include the treatment of generalised anxiety disorder.	26/06/2008	28/07/2008	SPC, Annex II, PL	Please refer to the Scientific Discussion: Cymbalta EMEA/H/C/572/II/27

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	Extension of Indication				
IB/0034	33_Minor change in the manufacture of the finished product	24/07/2008	n/a		
IB/0032	18_Replacement of an excipient with a comparable excipient	07/07/2008	n/a		
II/0029	Update of Summary of Product Characteristics sections 4.8 and 4.9. The Package Leaflet has been updated accordingly to reflect the changes. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2008	21/04/2008	SPC, Labelling, PL	The MAH following a search in their in-house clinical trial database as well as the post-marketing data from the spontaneous reporting has applied for changes in the section 4.8 "Undesirable effects" with the inclusion of new adverse drug reactions ("tinnitus", "gait disturbance", "poor quality sleep", "polyuria", "urine flow decreased", "sexual dysfunction" and "dermatitis contact") as well with the modification of the frequency in already known ones. In addition the cases for overdose have been reviewed and the wording has been modified in section 4.9 "Overdose" to include "coma" and "tachycardia" as symptoms of overdosing. The text was also amended to include signs and symptoms of overdosing observed with duloxetine alone or in combination with other medicinal products. Changes were implemented according to the latest QRD Template in the Product Information. The contact details of the representatives of Latvia have been updated.
IA/0030	22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	31/01/2008	n/a		
IB/0028	10_Minor change in the manufacturing process of the active substance	05/12/2007	n/a		
IB/0025	30_b_Change in supplier of packaging components - replacement/addition	30/08/2007	n/a		
II/0022	To update section 4.8 of the SPC regarding gastrointestinal bleedings and withdrawal symptoms, section 4.9 of the SPC regarding dosing and as requested by the CHMP and following discussions at the PhVWP to also update the wording on suicidality in section 4.4 of the SPC. The relevant sections of the Package Leaflet are amended accordingly. In	19/07/2007	28/08/2007	SPC, PL	Following the PSUR 4 (covering period 3 February 2006 to 2 August 2006) the MAH was requested to update the Product Information with the latest undesirable effects as well as the dosing of the product. In addition and following a meta-analysis published by the FDA regarding the suicidality of the patients administered duloxetine and further to scientific discussions at the PhVWP in June 2007 re-wording of that information has been performed in the section 4.4 of the SPC.

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	addition the contact details of the local representatives of Spain and Denmark have been updated. Update of Summary of Product Characteristics and Package Leaflet				
IB/0020	12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	08/06/2007	n/a		
IB/0024	14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	24/05/2007	n/a		
IA/0023	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	02/04/2007	02/04/2007	SPC, Labelling, PL	
IA/0021	11_b_Change in batch size of active substance or intermediate - downscaling	29/03/2007	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/2007	n/a	PL	
II/0017	The Marketing Authorisation Holder applied for an update of the Summary of Product Charasteristics (SPC) and the Package Leaflet (PL) following the review of the 3rd PSUR and review of duloxetine placebo-controlled clinical trial database. Sections 4.3, 4.4, 4.5, 4.6, 4.8, and 4.9 of the SPC and sections 2 and 4 of the PL have been amended. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	24/11/2006	SPC, PL	Summary Following the assessment of the third Periodic Safety Update Report (PSUR) the CHMP requested to the MAH to submit a variation to reflect the new safety information. In addition, the MAH also proposed some changes to the SPC following the review of the placebo-controlled clinical trial database. In this variation, the following sections have been updated: Section 4.3 - Contraindications Addition of contraindication with regards to the initiation of treatment in patients with uncontrolled hypertension. Section 4.4. Special warning and precautions of use In this variation warnings have been included in this section: -to update information on extrapyramidal disorders -to update information on blood pressure and heart rate. Section 4.5 Interaction with other medicinal products and other forms of interactions

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					This section was updated to state that ''Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelets drugs due to an increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin". In addition to this, the following information has been included: Duloxetine is an inhibitor of CYP2D6 and therefore caution is advised when duloxetine is co-administered with medicinal products predominantly metabolised by this route (i.e. risperidone, tricyclic antidepressants such as nortriptyline, amitriptyline, and imipramine). Section 4.6 Pregnancy and Lactation Section 4.6 was updated to reflect that duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients. Section 4.8 Undesirable effects The following Adverse Drug Reactions (ADRs) have been included in the section 4.8: Hypertensive crisis, supraventricular arrhythmia mainly, atrial fibrillation, paresthesia, hepatic failure, trismus, mania. In addition to this, the MAH updated the frequency of ADRs in section 4.8 to reflect the most recent clinical trials data. The Package Leaflet was updated to reflect the above changes.
II/0016	Change(s) to the manufacturing process for the active substance	27/07/2006	18/08/2006		
II/0013	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) to include new safety information following the review of the 2nd PSUR and results from a pharmacokinetic study in lactating women. Additional changes in the SPC and PL have been made. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	31/05/2006	SPC, Annex II, Labelling, PL	Following the assessment of the second Periodic Safety Update Report (PSUR) the CHMP identified a number of adverse reactions clinical relevant and which were not yet reflected in the Product Information. Therefore the MAH was requested to submit a variation to reflect the new safety information. In this variation warnings have been included in section 4.4 of the SPC: - to recommend caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure - to update information on withdrawal syndrome seen on discontinuation of treatment - to update information on extrapiramidal disorders

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					Section 4.8 (Undesirable Effects) of the SPC was also updated with regards to withdrawal symptoms and on the effects of duloxetine in Hb1Ac. In addition, the following ADRs have been added to section 4.8: chest pain, seizures, hypertension, hallucinations, akathisia, psychomotor restlessness. Section 4.5 of the SPC (Interaction with other medicinal products) was updated to state that "Increases in INR have been reported when duloxetine was co-administered with warfarin" and to include some examples of drugs metabolised by CYP2D6 with a narrow therapeutic range (such as flecainide, propafenone and metoprolol) in which case caution is advised if Cymbalta is co-administered. In this variation the MAH also update sections 4.6 and 5.2 of the SPC to reflect the results of a pharmacokinetic study in lactating women. The Package Leaflet was updated to reflect the above changes.
IA/0015	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/04/2006	25/04/2006	SPC, Labelling, PL	
IA/0014	08_a_Change in BR/QC testing - repl./add. of batch control/testing site	19/04/2006	n/a		
II/0010	This variation relates to an update of sections 4.4 and 4.8 of the SPC with safety information following assessment of PSUR 1 and a minor addition to section 4.7 concerning the potential for dizziness, with consequential changes to the relevant sections of the PL. Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	29/03/2006	SPC, PL	The MAH has updated the SPC and PL with safety information following assessment of the first Periodic Safety Update Report (PSUR). During the assessment of PSUR 1, 3 cases of SIADH (Severe Inappropriate Anti-Diuretic Hormone secretion), 7 cases of hyponatremia and 7 cases of blood sodium decreased were reported. These cases involved elderly patients (mean 76 years). In a number of cases risk factors were identified (pre-existing low level of blood sodium, renal failure, concomitant treatment with ACE or diuretics). Information has been added to section 4.4 of the SPC on that caution is required in patients at increased risk of hyponatraemia such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatraemia may reflect a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). During the assessment of PSUR 1, 12 cases of gastrointestinal

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					bleeding were reported. In a number of cases risk factors were identified. Nevertheless, there are a number of epidemiological studies showing that drugs that inhibit 5HT re-uptake increase the risk of bleeding, including gastrointestinal bleeding. Information has been added to section 4.4 of the SPC on that reports of gastrointestinal haemorrhage has been seen. As an increase in approximately 2 mmHg mean increase in blood pressure has been seen in patients treated with duloxetine, information is added to section 4.4 of the SPC on that duloxetine is associated with an increase in blood pressure in some patients. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate. Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). The pattern of liver damage was predominantly hepatocellular. This information was included in the SPC and it was recommended that duloxetine should be used with caution in patients with substantial alcohol use or with other drugs associated with hepatic injury. It was also added to the SPC that besides an association with sedation, dizziness may occur and patients should therefore be cautioned about their ability to drive a car or operate hazardous machinery when taking duloxetine. The following adverse drug reactions seen in clinical trials and/or been reported post-marketing were added to the SPC: hepatitis, elevated liver enzymes (ALT, AST, alkaline phosphatase), jaundice, syncope (especially at the initiation of treatment), orthostatic hypotension (especially at the initiation of treatment), extrapyramidal symptoms, serotonin syndrome, convulsions, anxiety and nervousness, dizziness, urinary retention, rash, anaphylactic reaction, angioneurotic oedema, Steven-Johnson syndrome, urticaria, hyponatraemia, SIADH, and glaucoma. The PL was also updated to reflect the above information.
IB/0012	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	01/12/2005	01/12/2005	SPC, Labelling, PL	

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A18/0011	Procedure under Article 18 of Council Regulation (EEC) No. 2309/93, as amended, to review suicide-related behaviours in children and adolescents. Article 18 Review	23/06/2005	15/09/2005	SPC, PL	Please refer to Scientific conclusion Cymbalta-EMEA/H/A-18/652
IB/0008	38_c_Change in test procedure of finished product - other changes	21/07/2005	n/a		
IB/0009	38_c_Change in test procedure of finished product - other changes	21/07/2005	n/a		
II/0004	This variation relates to an update of sections 4.2, 4.4, 5.1 and 5.2 of the SPC with data from a clinical study on the efficacy and safety of duloxetine in the elderly and the very elderly. Update of Summary of Product Characteristics	26/05/2005	04/07/2005	SPC	The SPC was updated with data on that no dosage adjustment is recommended for elderly patients solely on basis of age, but that caution should be exercised when treating the elderly, especially with the maximum dose (120 mg/day) for which data are limited. A summary of the results of this study in elderly depressed patients was also added to the SPC.
II/0003	The variation relates to an update of the section 4.1 of the SPC to include the indication “Diabetic Peripheral Neuropathic Pain (DPNP) in adults”. Consequential changes were introduced in sections 4.2, 4.4, 4.8 and 5.1 of the SPC and corresponding sections of the PL. Extension of Indication	26/05/2005	04/07/2005	SPC, PL	Please refer to Scientific Discussion: H-527-II-03.
IB/0007	42_a_01_Change in shelf-life of finished product - as packaged for sale	22/06/2005	n/a	SPC	
IB/0006	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	20/05/2005	20/05/2005	SPC, Labelling, PL	
IA/0005	22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/03/2005	n/a		
IA/0002	43_a_01_ Add./replacement/del. of	28/02/2005	28/02/2005	SPC, Labelling,	

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	measuring or administration device - addition or replacement			PL	
IB/0001	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release, IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	03/02/2005	n/a		