B.2 Listing of all direct randomised trials

B.2.1 Direct randomised trials: search results

Table B.2.1 summarises the search results for direct randomised trials.

Table B.2.1:[b]Summary of identification of direct randomised trials from the search of the published literature[c]

	Embase and Medline	PubMed	MEIP	CCTR	ACTR	Cochr. Libr.	Lundbeck datab. + TGA[d]	Conf. Abstr.	HTA Datab.	Hand Search.	Total
Total number of citations retrieved	9	9	2	0	0	7	10	1	0	0	39
Total number of duplicates	6	1	1			3	7				19
Total number of citations reviewed for inclusion	3	8	1	0	0	4	3	1	0	0	20
Number of citations excluded after title/abstract review:	1	5	1					1			8
• Not an RCT	1	2	1					1			5
• RCT does not include comparator		3									3
• Trial subjects are not representative of the proposed indication relevant/insufficient outcomes											
Number of citations excluded after full text review:	2					4					6
• RCT does not include comparator											
• Other	2					4					6
Number of citations of direct randomised trials included from each database		3									3
Number of direct randomised trials identified for inclusion in this submission	0	3	0	0	0	0	3[e]	0	0	0	6

ACTR = Australian Clinical Trials Registry, CT = Clinical Trials, EBM Databases (Includes: CDSR = Cochrane Database of Systematic Reviews, CENTRAL = Cochrane Central Register of Controlled Trials, CSA = Conference Papers Index, DARE = Database of Abstracts of Reviews of Effects), MIP = Medline-In-Process

[b] Tables B2.1 and B2.2 of the Guidelines have been combined into this table to account for the duplicates and the final number of RCTs included in this submission.
[c] Same as Table 12 in Attachment 4.
[d] The conference presentations relating to the study reports are reported as duplicates. However all 3 study reports are utilised in the submission.
[e] There are 3 study reports and the identified PubMed articles that are the representative publications of these trials.

B.2.2 Master list of trials

Table B.2.2 provides a list of trials (and associated reports) presented in the submission.

Table B.2.2:Trials (and associated reports) presented in the submission

Trial ID	Report	Study Included in Original Submission
99270	Integrated Clinical Study Report: A double-blind, randomised trial comparing the efficacy and safety of fixed dosages of Lu 26-054 and paroxetine with placebo in the treatment of patients with Social Anxiety Disorder (Report No. 266-311, 2002; dated 14 March 2003).	Yes
	Lader et al, 2004:[1] Lader M, Stender K, Burger V, Nil R. Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: Randomised, double-blind, placebo-controlled, fixed-dose study. Depression and Anxiety 2004;19(4):241-248.	
	Montgomery et al 2003(abstract)[2] Montgomery SA., Lader M., Nil R., Escitalopram and paroxetine in fixed doses for the treatment of social anxiety disorder (SAD). Nordic Journal of Psychiatry, 2003 (a)	
	Montgomery et al 2003(abstract)[3] Montgomery SA., Lader M., et al., Escitalopram and paroxetine in fixed doses for the treatment of social anxiety disorder (SAD). 4th Annual Meeting of the Scandinavian College of Neuro-Psychopharmacology, 9-12 April 2003, France	
99012	Integrated Clinical Study Report: A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 in the treatment of patients with social anxiety disorder (Report No. 226/311, 2000; dated 18 July 2002)	No New Study
	Kasper et al 2005[4]: Kasper S, Stein DJ, Loft H, Nil R. Escitalopram in the treatment of social anxiety disorder: Randomised, placebo-controlled, flexible-dosage study. British Journal of Psychiatry 2005;186(MAR.):222-226.	

	Kasper et al, 2002a[5] Kasper S., Loft H., Smith JR., Escitalopram is well tolerated in the treatment of social anxiety disorder. Anxiety disorders association of America (ADAA). March 2002.	
	Kasper et al 2002b[6] Kasper S., Loft H., Nil R., Escitalopram is well tolerated in the treatment of social anxiety disorder. Scandinavian College of Neuropsychopharmacology (SCNP), April 2002	
	Kasper et al 2002c[7] Kasper S., Escitalopram is well tolerated in the treatment of social anxiety disorder. American Psychiatric association (APA), May 2002	
	Kasper et al 2002d[8] Kasper S., Loft H., Nil R., Treatment of social anxiety disorder: Escitalopram is well tolerated and efficacious. Collegium Internationale Neuro-Psychopharmacologicum (CINP), June2002	
	Kasper et al 2002e[9] Kasper S., Loft H., Smith JR., Escitalopram is efficacious and well tolerated in the treatment of SAD. Association of European Psychiatrists (AEP), May 2002.	
99269	Integrated Clinical Study Report: A double-blind, randomised, placebo-controlled, flexible-to fixed-dose relapse prevention study with Lu 26-054 in Social Anxiety Disorder (Report No. 226/311, 2000; dated 18 July 2002)	No New Study
	Montgomery et al 2005[10]: Montgomery SA, Nil R, Durr-Pal N, Loft H, Boulenger JP. A 24-week randomized, double-blind, placebo-controlled study of escitalopram for the prevention of generalized social anxiety disorder. Journal of Clinical Psychiatry 2005;66(10):1270-1278.	
	Montgomery et al 2005[11]: Relapse Prevention in Patients Suffering From Social Anxiety Disorder. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26.	

All study details and results are taken from the Clinical Study Reports (rather than the published papers) as these contain the most comprehensive details and results for the studies. The details reported in the cited published papers have been compared with the study reports and any discrepancies are detailed in the relevant part of Section B of the submission.

B.2.3 Exclusion of trials

All trials identified in the literature search and excluded from the submission are listed in Table B.2.3 (this is based on Table 11 in Attachment 4; where the full list and details of inclusion or exclusion can be found).

Table B.2.3:Reasons to exclude each direct randomised trial from the submission

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
Atmaca, M., E. Tezcan, et al. (2004). "Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment." Eur Arch Psychiatry Clin Neurosci 254(4): 231-5.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
Atmaca, M., M. Kuloglu, et al. (2002). "Efficacy of citalopram and moclobemide in patients with social phobia: some preliminary findings." Hum Psychopharmacol 17(8): 401-5.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
Bandelow, B., D. S. Baldwin, et al. (2006). "What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder?" Journal of Clinical Psychiatry 67(9): 1428-1434	Review	Not an RCT	Table 11; Attachment 4
Bouwer, C. and D. J. Stein (1998). "Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia." J Affect Disord 49(1): 79-82.	Not a relevant comparator	Not a relevant comparator	Table 11; Attachment 4
Davidson, J., Pharmacotherapy of social anxiety disorder: What does the evidence tell us? Journal of Clinical Psychiatry, 2006. 67: p. 20-26.	Review	Not an RCT	Table 11; Attachment 4
Dhillon, S., L. J. Scott, et al. (2006). "Escitalopram: A review of its use in the management of anxiety disorders." CNS Drugs 20(9): 763-790.	Review	Not an RCT	Table 11; Attachment 4

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
Hedges, D. W., B. L. Brown, et al. (2007). "The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: A meta-analysis of double-blind, placebo-controlled trials." Journal of Psychopharmacology 21(1): 102-111.	Meta-analysis of all SSRIs for SAD. The study that included escitalopram is Lader M. et al (2004) which is included in the current submission.	Meta-analysis of SSRIs in social anxiety disorder – not all comparators used are appropriate. Lader M. et al (2004) which is included in the meta-analysis is included in this submission.	Table 11; Attachment 4
Ipser, J.C., P; Dhansay, Y; Fakier, N; Seedat, S; Stein, DJ, Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews., 2007. 2.	Meta-analysis of pharmacotherapy for SAD. The study that included escitalopram is Kasper (2002), which is included in the current submission.	Meta-analysis of pharmacotherapy in social anxiety disorder – not all comparators used are appropriate. Kasper S (2002) which is included in the meta-analysis is included in this submission as Kasper S (2005).	Table 11; Attachment 4
Montgomery SA. Relapse Prevention in Patients Suffering From Social Anxiety Disorder. in 158th Annual Meeting of the American Psychiatric Association. May 2005. Atlanta, GA.	Same as Montgomery 05	Poster presentation of Montgomery 05	Table 11; Attachment 4
Pallanti, S. and L. Quercioli (2006). "Resistant social anxiety disorder response to Escitalopram." Clinical Practice and Epidemiology in Mental Health 2:35.	Open label, non-randomised	This was a 12 week open trial of escitalopram treatment for patients who had failed other treatments.	Table 11; Attachment 4

Trial ID	Ground(s) for seeking exclusion	Details[a]	Source
Stein, D.I., JC; van Balkom, AJ, Pharmacotherapy for social anxiety disorder. Cochrane Database of Systematic Reviews, 2007. 2.	Review article.	All studies reviewed are included in the submission (Kasper et al, 2002).	Table 11; Attachment 4
Stein, D. J., E. W. Andersen, et al. (2006). "Escitalopram versus paroxetine for social anxiety disorder: An analysis of efficacy for different symptom dimensions." European Neuropsychopharmacology 16(1): 33-38.	Re-analysis of Lader et al (2004; Study 99270) looking at different symptom dimensions	Lader et al (2004) is included in the submission	Table 11; Attachment 4

TableB.2.4 summarises the key design and population characteristics of the three identified trials, and also the main primary and secondary outcomes.

TableB.2.4:Comparative summary of characteristics of direct randomised trials

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
Included trials					
99270	RCT, DB, MN, MC, FD	placebo escitalopram: 5, 10, 20mg/day paroxetine: 20mg/day 24 weeks	N=840 • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • SDS subscale ≥5 • Exhibited fear or avoidance in at lease four social situations (derived from baseline LSAS) • Age: 18-65	Efficacy from the baseline to wk12 is LSAS total score using LOCF Safety AEs, DESS checklist, clinical safety laboratory tests, ECGs, vital signs, weight, and physical examinations	• Change from baseline to each visit in LSAS total score • Change from baseline to final assessment in LSAS subscale (fear/anxiety, avoidance) score • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with CGI-I score ≤ 2 per visit • Proportion of patients with CGI-S score ≤ 2 per visit • Change from baseline to each visit in SDS items 1-3 score • Assessment of depression status – change from baseline to each visit in MADRS total score
99012	RCT, DB	placebo escitalopram: 10- 20mg/day 12 weeks	N=358 • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • CGI-S score≥4 • Has a score ≥2 on at least 4	Efficacy Change from the baseline to final assessment of the LSAS total score using LOCF Safety AEs, clinical safety laboratory tests, ECGs, vital signs and physical	• Change from baseline to each visit in LSAS total score • Change from baseline to last assessment in LSAS subscale (fear/anxiety, avoidance) total score • CGI-S score per visit • Change from baseline to each visit in CGI-S score

Trial ID	Design characteristics [a]	Compared interventions (*N*, drug, dose, frequency, duration)	Summary of main population characteristics	Main outcomes	
				Primary	Secondary
			items of both the fear and avoidance questions on the LSAS rating at screening and at baseline • Exhibited fear or avoidance in at lease four social situations (derived from baseline LSAS) • Age: 18-65	examinations	• CGI-I score per visit • Proportion of patients with CGI-I score ≤ 2 • Change from baseline to each visit in SDS items 1-3 score • Assessment of depression status – change from baseline to each visit in MADRS total score
99269	RCT, DB, MN, MC, Flexible to fixed dose 12 wk open label and a 24 wk double-blind period	placebo escitalopram: 10- 20mg/day	N=517 open label N=372 DB period • DSM-IV criteria for a primary diagnosis of generalised SAD • LSAS≥70 • SDS subscale ≥5 • Exhibited fear or avoidance in at lease four or more social situations (derived from baseline LSAS) • Age: 18-80	<u>Efficacy</u> Time to relapse in the double-blind period <u>Safety</u> AEs, DESS checklist, clinical safety laboratory tests, ECGs, vital signs, weight, and physical examinations	LSAS CGI-I CGI-S SDS

AE = adverse events; C-O = cross-over; DB = double-blind; DBP = diastolic blood pressure; ITT = intention to treat; MC = multicentre; MN = multinational; PG = parallel group; PP = per protocol analysis; RCT = randomised controlled trial; LOCF= last observation carried forward

B.3 Assessment of the measures taken by investigators to minimise bias in the direct randomised trials

Summary

The three key studies were all studies providing the highest level of evidence. They were randomised, double-blind, parallel-group, multicentre direct comparisons of escitalopram and placebo. Randomisation was provided off-site by a third party, identical study product was provided for each group and patients, investigators and assessors were fully blinded treatment assignment. Full details of the adequacy of randomisation and blinding are provided. Intention-to-treat (last observation carried forward) analysis was used, with full details of patient follow-up provided.

All the information provided in Section B.3 was sourced from the Clinical Study Reports for Study 99270, Study 99012 and Study 99269. These reports are provided in electronic form on the CD-ROM labelled Clinical Study Reports and References. Hard copies of the Study Reports are also provided.

B.3.1 Randomisation

The patients in the studies were all randomised, following a run-in period. As Study 99269 was a relapse prevention study, all patients received open-label escitalopram for 12-weeks prior to randomisation. With this type of study all patients have to receive treatment to allow them to respond to treatment so that the efficacy of the antidepressant agent with regard to relapse prevention can be compared to placebo in the double-blind phase of the study.

Patients admitted to the double-blind period in all three studies were randomly allocated to either placebo or escitalopram according to a randomisation code generated by Lundbeck. Randomisation numbers and study product were prepared, equally assigned to each treatment group (2 groups in 99269, 99012 and 5 groups in 99270). Block randomisation was used in all the studies, to ensure that equal numbers

of patients entered each treatment group. At each centre the 4-digit randomisation number was to be assigned consecutively, starting with the lowest number available.

B.3.2 Blinding

The studies were all double-blind. The study products were encapsulated tablets for oral administration in Studies 99270 and 99269. In Study 99012 identical active and placebo tablets were used. Patients took either one or two tablets daily, equivalent to escitalopram 10mg or 20mg daily in the active group. All tablets were oval, white, scored and film-coated (not specified in 99269). All capsules were identical. The randomisation code was not broken in Studies 99270 or 99012. In Study 99269 the randomisation code was broken for one patient, after the patient had stopped treatment with placebo.

B.3.3 Adequacy of follow-up

Studies 99270 and 99012

The following analysis sets were defined *a priori*:

- All-patients-randomised set (APRS) – all patients randomised into the study
- All-patients treated set (APTS) – all randomised patients who took at least one dose of double-blind study product
- Full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the LSAS total score
- Per-protocol set (PPS) – all randomised patients who had no major protocol violations (as pre-defined in the Statistical Analysis Plan), who received double-blind study product at least up to Week 4, and who had at least one post-baseline assessment of the LSAS total score at or after Week 4.

All efficacy analyses were conducted on the FAS. Note that the primary study outcome is a continuous variable and it is therefore necessary to have at least one

post-baseline assessment to allow a valid result to be recorded for that patient. All safety analyses were conducted on the APTS.

In both studies all efficacy analyses, including the primary analysis of the change in LSAS total score over the study period was based on the FAS using last observation carried forward (LOCF).

Study 99269

The following analysis sets were defined *a priori*:

- All-patients treated set (APTS) – all patients enrolled in the open-label period who took at least one dose of study product
- All-patients-randomised set (APRS) – all patients randomised into the study
- Full-analysis set (FAS) – all randomised patients who took at least one dose of double-blind study product.
- Per-protocol set (PPS) – all randomised patients in the FAS who did not relapse or withdraw at or before Day 7 and omitting all subsequent assessments for patients committing major protocol violations.

All efficacy analyses were conducted for the FAS and, when considered relevant, also for the PPS. All safety analyses were based on the APTS and the FAS for the open-label and double-blind periods, respectively.

The primary analysis of efficacy consisted of a log-rank test on the FAS comparing the time to relapse for the escitalopram and the placebo groups. Actual treatment days were used in the analysis, which was supplemented with Kaplan-Meier plots.

A summary of the measures taken to minimise bias in the key studies is presented in TableB.3.1.

TableB.3.1:Summary of the measures undertaken to minimise bias in the direct randomised trials

Trial ID	Concealment of randomisation[a]	Blinding			Basis of analysis[b]
		Participants	Investigators	Outcomes assessors	
99270	B (p. 27)	Yes (p. 21)	Yes (p. 21)	Yes (p. 21)	E[c] (p. 39, 41)
99012	B (p. 25)	Yes (p. 20)	Yes (p. 20)	Yes (p. 20)	E[c] (p. 36, 39)
99269	B (p. 27)	Yes (p.21)	Yes (p.21)	Yes (p.21)	E[d] (p. 41, 43)

All page references are for the relevant Study Report.
a A = central telephone randomisation service; B = third-party randomisation service (eg pharmacy, pharmaceutical company);
C = sequentially labelled, fully opaque, sealed envelopes
b D = intention-to-treat (all randomised participants: specify how the analysis dealt with missing data); E = all treated participants (specify how the analysis dealt with missing data); F = per protocol participants; G = other (specified)
c The study population consisted of all patients randomised to treatment who took at least one dose of double-blind study medication and who had at least one valid post-baseline assessment of the primary efficacy variable (LSAS total score). Last observation carried forward (LOCF) methodology was used for missing data. All safety analyses were conducted on all patients who took at least one dose of study medication
d. The study population (efficacy and safety) consisted of all patients randomised to treatment who took at least one dose of double-blind study medication. Last observation carried forward (LOCF) methodology was used for missing data.

Details of the flow of patients through the direct randomised trials are presented in TableB.3.2.

TableB.3.2:Flow of participants through the direct randomised trials

Trial ID • Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Dis-continued	Analysed
99270[a]					
• Escitalopram 10mg	168	1 (0.6%)	7 (4.2%)	60 (35.9%)	164 (97.6%)[b]
• Escitalopram 20mg	170	0 (0%)	7 (4.1%)	54 (31.8%)	163 (95.9%)[b]
• Placebo	166	0 (0%)	5 (3.0%)	54 (32.5%)	165 (99.4%)
99012					
• Escitalopram	181	0 (0%)	8 (4.4%)	36 (19.9%)	177 (97.8%)
• Placebo	177	0 (0%)	5 (2.8%)	32 (18.1%)	176 (99.4%)
99269					
• Escitalopram	190	0 (0%)	3 (1.6%)	64 (33.7%)	190 (100%)
• Placebo	182	1 (0.6%)	2 (1.1%)	101 (55.5%)	181 (99.5%)

a. Information on the escitalopram 5mg daily and paroxetine treatment arms are not presented, as they are not relevant to this submission. Full details are available in the Clinical Study Report provided.
b. The published paper[12] reports that there are n=162 patients in the escitalopram 10mg and 20mg arms full analysis set population. It is unclear why this differs from the numbers reported in the Clinical Study Report.

Source:
Study 99278 - Panel 7 p.45, Panel 9 p.47
Study 99012 - Panel 6 p.42, Panel 7 p.43
Study 99269 - Panel 10 p.48, Panel 11 p.49

Source Documents

The study reports for the three direct randomised trials are the source documents for all information in this section. The page references for all the information are provided under or in TableB.3.1and TableB.3.2.

B.4 Characteristics of the direct randomised trials

Summary

This resubmission included two new studies: Study 99012 and 99269. This meant that the effective duration of therapy for assessment was 48 weeks (24 weeks for Study 99270 and an additional 24 weeks from the relapse prevention study 99269); a total of 70 weeks of data for SAD patients on escitalopram. s38

The key randomised, controlled studies (Study 99270, 99012 and 99269 all included patients diagnosed with moderate to severe SAD whose lives were severely disrupted because of fear and avoidance of normal social situations. Patients did not have other psychiatric co-morbidities.

The studies were all parallel group, randomised controlled trials of 12 week (Study 99012) or 24 week (Study 99270) duration. Study 99269 was a relapse prevention study with patients receiving 12 weeks of open-label escitalopram, with responders then randomised to receive a further 24 weeks therapy with either escitalopram or placebo. Patients were randomised to either a fixed dose of escitalopram or placebo (Study 99270), or a flexible dose of escitalopram dose (Study 99012 and 99269). Full details of the interventions received are presented in Section B.4.2, including details of the actual escitalopram doses taken.

The baseline characteristics of patients (age, sex, race, duration and onset of SAD) across the studies and in the treatment arms within studies were all similar.

The characteristics of patients included in the key randomised, controlled trials are presented in Section B.4. The eligibility criteria are detailed followed by the baseline demographic and clinical characteristics of the patients. The study designs are explained, including the daily dose of the interventions received in each treatment group (escitalopram and placebo) and the duration of the trials. All trials have been

completed. Full details of each study are available in the Study Report provided, with clear cross-referencing in this submission to the relevant pages and tables.

A summary of the trial characteristics for the key studies included in this submission (Studies 99270, 99012 and 99269) is provided in TableB.4.1.

TableB.4.1:Summary of the characteristics of the included trials (Study 99270, 99012 and 99269)

Trial ID	Design / Duration	Size	Location	Dosage regimen	Trial population
99270	Randomised, double-blind, placebo-controlled, parallel group, fixed dose study comparing 3 ESC doses, paroxetine and placebo - 1 week run-in - 24 week randomised phase - 2 week placebo run-out period	840 patients ESC 10 167 ESC 20 170 Placebo 166	47 centres in 11 countries in Europe, including the UK	Relevant study arms: ESC 10mg once daily ESC 20mg once daily Placebo once daily Other study arms: ESC 5mg daily Paroxetine 20mg daily	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities
99012	Randomised, double-blind, placebo-controlled, parallel group, flexible dose study comparing ESC and placebo - 1 week run-in - 12 week randomised phase	358 patients ESC 181 Placebo 177	41 centres in 8 countries in Europe (including UK), Canada, South Africa	- ESC once daily – initially 10mg once daily, increased to 20mg daily if required after Week 4. - Placebo once daily	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities
99269	Randomised, double-blind, placebo-controlled, parallel group study, flexible dose, relapse prevention study comparing ESC and placebo - 12 week open label period - 24 week randomised, double-blind period	372 patients ESC 190 Placebo 182	76 centres in 11 countries in Europe (including UK), Canada, South Africa	Open-label period: - Initially ESC 10 once daily, which could be increased to 20mg once daily if required. Double-Blind period: - ESC 10 or 20mg once daily (i.e. dose patient was on in open-label phase) - Placebo	Adult SAD patients (DSM IV diagnosis) Moderate to severe disability (based on LSAS, SDS, CGI-S scale scores) Exhibited fear and avoidance traits in social situations (based on LSAS score) No co-morbidities

CGI-S = Clinical Global Impression – Severity; ESC = escitalopram; LSAS = Liebowitz Social Anxiety Scale; SDS = Sheehan Disability Scale

B.4.1 Selection of the study population

The key studies included adult patients with SAD diagnosed based on DSM-IV criteria. These patients had a Liebowitz Social Anxiety Score (LSAS) of 70 or more. The LSAS is designed to assess SAD through evaluation of fear and avoidance in social situations. A minimum entry score of at least 70 in SAD investigational drug studies is recommended to ensure that patients have moderate to severe SAD (European College of Neuropsychopharmacology (ECNP) Guidelines, 2003[13]). For study inclusion patients also had to experience fear and avoidance in at least four distinct social situations (based on LSAS baseline scores) to ensure that patients had the more severe generalised form of SAD[13].

Patients were excluded from study entry if they suffered from other psychiatric disorders or co-morbidities. While patients with SAD often do suffer from co-morbidities such as alcohol/substance abuse and depression, it is usual to exclude or control for the confounding variable (i.e. the co-morbidity) which may affect the results. The ECNP Guidelines recommend that "*In all cases the primary diagnosis should be SAD and patients with other recent or current psychiatric diagnoses should be excluded"*[13].

The ECNP Guidelines further state that "*In studies that include a putative or potential antidepressant, patients suffering from concomitant major depression as well as those with a history of major depression over the previous 3-6 months, should be excluded. Some "depressive symptoms" are part of SAD. However current depressive symptoms should nevertheless be restricted to a mild level, with a maximum permitted score on a depression rating scale below that normally used to include patients into depression studies. The results of these studies may then be generalisable to the population with SAD without concerns of an indirect effect via depression*"[13]. The Montgomery and Åsberg Depression Rating Scale (MADRS) was administered to patients in order to exclude patients with depression from the key studies.

The inclusion and exclusion criteria for the direct randomised trials are presented in TableB.4.2.

TableB.4.2: Eligibility criteria in the direct randomised trials

Trial ID	Inclusion criteria	Exclusion criteria
99270	Age: 18-65 years	Any other Axis I diagnosis that was considered the primary disorder or the predominant disorder (over the last 6 months).
	Patient was an outpatient	Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study.
	Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD	Patient had a baseline MADRS total score ≥18.
	Patient had a total LSAS score ≥70	Patient had an alcohol or drug abuse problem, as defined in DSM-IV.
	Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS)	Patient suffered from mania or hypomania or had a history thereof, as defined in DSM-IV.
	Patients were otherwise healthy	Patient suffered from body dysmorphic disorder, as defined in DSM-IV.
	Gave informed consent and willing to attend study appointments in the correct time windows	Patient had an Axis II Cluster B diagnosis: antisocial personality disorder, borderline personality disorder, histrionic personality, or narcissistic personality disorder.
	Patient had a score ≥5 on one or more of the SDS subscales	Patient suffered from MDD, panic disorder, or obsessive compulsive disorder, as defined in DSM-IV.
		Patients with schizophrenia, as defined in DSM-IV, or any other psychotic disorder or history thereof.
		Female patients of child bearing potential who were pregnant or breastfeeding or not using adequate contraception.
		Patients suffering from eating disorders, as defined in DSM-IV.
		Patients suffering from mental retardation or other cognitive disorder.
99012	Age: 18-65 years	Any other Axis I diagnosis that was considered the primary diagnosis.
	Patient was an outpatient	Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study.
	Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD	Patient had a baseline MADRS total score >19.
	Patient had a total LSAS score ≥70 and a CGI-S rating of ≥4 at baseline.	Patient had an alcohol or drug abuse problem, as defined in DSM-IV within 6 months prior to screening.
	Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS). At least 2 of these were required to involve interpersonal interactions.	Patient had an Axis II Cluster A diagnosis: personality disorder or borderline or antisocial personality disorder.

Trial ID	Inclusion criteria	Exclusion criteria
	Patients scored at least 2 on at least 4 items of the fear and avoidance questions on the LSAS rating at screening and baseline. Patients were otherwise healthy Gave informed consent and willing to attend study appointments in the correct time windows	Patient suffered from mania or hypomania, body dysmorphic disorder, schizophrenia or any other psychotic disorder, or eating disorders as defined in DSM-IV. Female patients of child bearing potential who were pregnant or breastfeed or not using adequate contraception. Patients suffering from mental retardation or other cognitive disorder. Patients using any of the listed disallowed therapies. Patients with a lack of response to citalopram treatment for SAD at a dose and duration normally adequate to show a response (previous and current episodes included). Patient at serious risk of suicide (investigators opinion) Patients with hypersensitivity to citalopram or with a history of severe drug allergy or hypersensitivity. Patients had a serious illness (according to the list provided). Patients unlikely to comply with the study protocol or was considered unsuitable (investigator's opinion). Patient had a positive drug screen result at screening. Patient was rated <3 (mildly ill) on the CGI-S scale at Visit 1 and 2.
99269	Age: 18-80 years Patient was an outpatient Fulfilled the DSM-IV criteria for a primary diagnosis of generalised SAD Patient had a total LSAS score ≥70 Exhibited fear or avoidance traits in at least 4 social situations (derived from baseline LSAS) Patients were otherwise healthy Gave informed consent and willing to attend study appointments in the correct time windows Patient had a score ≥5 on one or more of the SDS subscales	Any other Axis I diagnosis that was considered the primary disorder or the predominant disorder (over the last 6 months). Receiving formal psychotherapy and/or cognitive behavioural therapy or was planning to initiate such therapy during the study. Patient had a baseline MADRS total score ≥18. Patient had an alcohol or drug abuse problem, as defined in DSM-IV. Patient suffered from mania or hypomania or had a history thereof, as defined in DSM-IV. Patient suffered from body dysmorphic disorder, as defined in DSM-IV. Patient had an Axis II Cluster B diagnosis: antisocial personality disorder, borderline personality disorder, histrionic personality, or narcissistic personality disorder. Patient suffered from MDD, panic disorder, or obsessive compulsive disorder, as defined in DSM-IV. Patients with schizophrenia, as defined in DSM-IV, or any other psychotic disorder or history thereof.

Trial ID	Inclusion criteria	Exclusion criteria
		Female patients of child bearing potential who were pregnant or breastfeeding or not using adequate contraception. Patients suffering from eating disorders, as defined in DSM-IV. Patients suffering from mental retardation or other cognitive disorder. Patients using any of the listed disallowed therapies. Patients with a lack of response to previous treatment for SAD with SSRI. Patient at serious risk of suicide (investigators opinion or scored ≥5 points on item 10 of MADRS) Patients with hypersensitivity to citalopram and/or escitalopram or with a history of severe drug allergy or hypersensitivity. Patients had a serious illness (according to the list provided). Patients unlikely to comply with the study protocol or was considered unsuitable (investigator's opinion).

Source: 99269 Study Report p. 23-25.
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; LSAS = Liebowitz Social Anxiety Scale; MADRS = Montgomery and Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale

B.4.2 Trial dosage regimens

Two of the studies (99012 and 99269) used flexible doses of escitalopram, with patients commencing on 10mg daily and investigators able to increase the dose to 20mg daily (see Section B.4.4 – Study Design for full details). The actual escitalopram doses used in the flexible dose studies (the average daily dose) are presented following TableB.4.3 below. Study 99270 compared three fixed dosages of escitalopram, paroxetine 20mg daily and placebo. Only the relevant treatment arms (i.e. escitalopram 10mg and 20mg daily and placebo) are reported in the submission.

The Australian Approved Product Information (Attachment 1) for escitalopram use in SAD recommends commencing with 10mg daily, increasing to a maximum of 20mg daily if necessary. The study dosages reported are all within this approved range.

TableB.4.3 summarises the interventions compared in the included studies.

TableB.4.3: Interventions compared by the direct randomised trials

Trial ID	Treatment	Dosage regimen	Duration of treatment median (range)	Duration of follow-up Median (range)
99270[a]	ESC 10mg	ESC 10mg/day (1 capsule morning or evening[b]) for 24 weeks	168 days (1-217 days)[c]	NR
	ESC 20mg	ESC 20mg/day (1 capsule morning or evening[b]) for 24 weeks	168 days (1-202 days)[c]	NR
	Placebo	Placebo once daily (1 capsule morning or evening[b]) for 24 weeks	168 days (10-196 days)[c]	NR
99012	ESC	Escitalopram 10mg (1 tablet) once daily. After weeks 4, 6 or 8 the daily dose could be increased to 20mg daily or left at 10mg daily. Dosage could be decreased from 20mg daily to 10mg daily in the event of adverse events. The total double-blind treatment period was 12 weeks.	84 days (1-109 days)[c]	NR
	Placebo	Placebo (1 capsule) once daily. After weeks 4, 6 or 8 the daily dose could be increased to 2 tablets daily or left at 1 tablet daily. Dosage could be decreased from 2 tablets daily to 1 tablet daily in the event of adverse events. The total double-blind treatment period was 12 weeks.	84 days (2-99 days)[c]	NR
99269	ESC	ESC 10 or 20mg (1 tablet once daily, preferably in the morning) for 24 weeks[d].	168 days (7-194 days)[e]	NR
	Placebo	Placebo (1 tablet once daily, preferably in the morning) for 24 weeks[d]	112 days (5-190 days)[e]	NR

ESC = escitalopram; NR = not reported
Source:
Study 99270 – p. 26, Table 25;
Study 99012 – p. 20, 24, 25, Table 15
Study 99269 - p. 2, 26, Table 30;

a. the escitalopram 5mg daily treatment arm is not presented as it is not an approved dosage; the paroxetine 20mg daily arm, is also not presented as it not a comparator
b. at the same time every day, either morning or evening.
c. "All patients treated set" (APTS) population, i.e. all randomised patients who took at least one dose of double-blind study medication.
d. Patients received 12 weeks of open-label escitalopram – initially 10mg daily which could be increased to 20mg daily at Week 2, 4 or 8. The open-label period was designed to detect responders to escitalopram treatment. In the double-blind period patients were randomised to receive either escitalopram at the same dose that they were taking at the end of the open-label period or placebo, both once daily.
e. "Full analysis set" (FAS) population, i.e. all randomised patients who took at least done dose of double-blind study medication (the definition for FAS used in this study differs from that used in the other two studies).

B.4.3 Doses used in the clinical trials

Study 99270

Study 99270 used fixed doses of escitalopram or placebo as described in Table B.4.3.

Study 99012

There was a 1-week, single-blind run-in period with placebo, followed by a 12-week, double-blind treatment period with escitalopram or placebo. The initial dose of escitalopram was 10mg daily. At Week 4, 6 or 8 investigators had the option of doubling a patient's dosage of study product from 10mg to 20mg, if his/her response had been unsatisfactory or if there was an aggravation of the disorder based on the Clinical Global Impression Severity (CGI-S) score. Investigators could decrease the dosage to the original dosage at any time if there were adverse events.

The percentages of patients in each treatment group who had their dosage of study drug doubled from 10 to 20mg at Week 4, 6 or 8 were 68% for the escitalopram group and 69% for the placebo group (APTS population, i.e. all randomised patients who took at least one dose of double-blind study product). Of these, 4% of escitalopram-treated patients and 2% of placebo-treated patients had their dosage of study drug reduced to 10mg after dose increase. The majority of patients had their dosage doubled at Week 4 (escitalopram 61%, placebo 65%). (Source – Study Report 99012 p. 50 and Table 16). TableB.4.4 below reports the mean daily doses used in each treatment arm during the study. At the end of the treatment period patients on escitalopram were taking a mean dose of 17.1mg daily.

TableB.4.4:Doses used in Study 99012 (APTS population)

Week	ESC			Placebo	
	N	Mean capsules/day	Mean mg/day	N	Mean capsules/day
1	177	1.0	10.0	173	1.0
2	169	1.0	10.0	171	1.0
3	165	1.0	10.0	167	1.0
4	163	1.1	10.5	164	1.1
6	161	1.6	16.2	162	1.7
8	158	1.7	17.0	157	1.7
12	149	1.7	17.1	152	1.7

Source: Study Report 99012 Table 16
APTS = all patients treated set, i.e. patients who received at least one dose of study product.

Study 99269

All patients received escitalopram 10mg daily during the initial 12 week open-label period. The dosage could be increased to 20mg daily if clinically indicated at Week 2, 4 or 8. As the study was designed to assess relapse to escitalopram, only patients who responded to treatment in the open-label phase were then randomised into the double-blind phase that followed. Of those randomised, 139 escitalopram patients (out of 190 patients, or 73%) received 20mg daily and 141 placebo patients (out of 181, or 78%) received 2 placebo tablets daily[10]. This equates to a mean daily dose of escitalopram of 17.3mg.

B.4.4 Study design

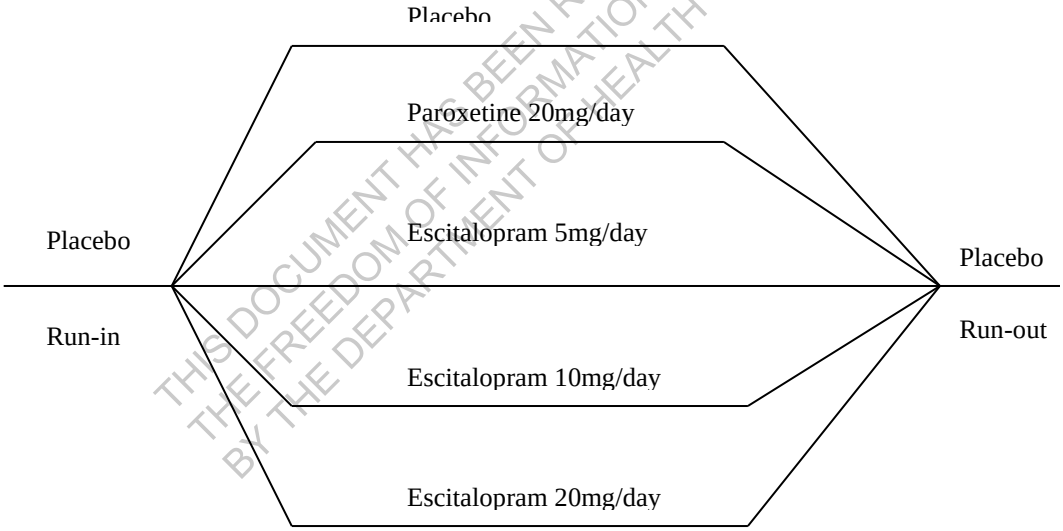
The efficacy and safety of escitalopram in SAD was investigated in three placebo-controlled clinical studies conducted as part of a comprehensive clinical development program:

a) A long-term fixed dose study (10mg or 20mg/day) – **Study 99270**
b) A shorter-term flexible dose (10-20mg/day) study - **Study 99012**
c) A flexible dose relapse prevention study – **Study 99269**

a) Study 99270

This was a multicentre, fixed-dose, randomised, double-blind, placebo-controlled, active-reference study with five parallel treatment groups. The study consisted of a 1-week single-blind placebo run-in period after which patients were randomised in a (1:1:1:1:1 ratio) to 24 weeks of double-blind treatment with fixed doses of escitalopram (5, 10 or 20mg/day), paroxetine (20mg/day) or placebo. The paroxetine arm results are not presented in this submission as it is not a comparator. The escitalopram 5mg daily treatment results are also not presented, as this is not an approved dosage for SAD in Australia. Patients who completed double-blind treatment entered a 2-week single-blind run-out period during which they received placebo. The overall study design is presented in Figure B.4.1.

Figure B.4.1: Overall study design (Study 99270)



Rationale for study design:

A double-blind, placebo controlled design is an expected design for investigating the efficacy and safety profile of a medication for this type of indication. The duration of 12 weeks for the acute treatment period was chosen since clinically and statistically significant improvements in SAD have been seen with other SSRIs within a 12-week

treatment period[14 15 16]. The treatment extension to 24 weeks was included to demonstrate whether the acute treatment effects were sustained, and to evaluate the response to therapy after an additional 12 weeks of treatment.

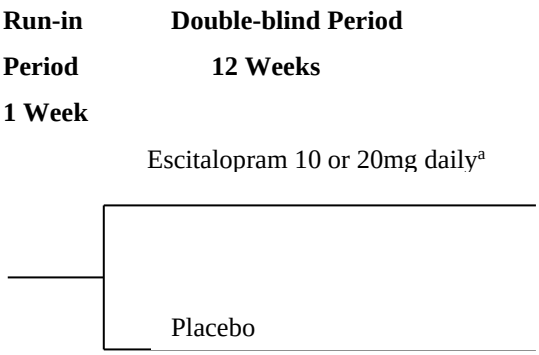
A one-week, single-blind, placebo run-in period allowed for the exclusion of patients who responded (Clinical Global Impression – Improvement (CGI-I) score of 1 or 2) to placebo therapy as well as washout psychoactive medication, which had been taken prior to screening and which may have influenced social behaviour. It also provided time for the assessment of clinical safety laboratory test results and electrocardiograms (ECGs). A two-week, single-blind, placebo run-out period was included to examine potential treatment withdrawal reactions.

b) Study 99012

This study was a multinational, randomised, double-blind, parallel-group, placebo controlled flexible-dose study. There was a one-week single-blind run-in period with placebo, followed by a 12-week, double-blind treatment period with escitalopram or placebo. The initial dose of escitalopram was 10mg daily. At Week 4, 6 or 8 investigators had the option of doubling a patient's dosage of study product from 10 to 20mg daily if his/her response had been unsatisfactory or if there was an aggravation of the disorder based on the Clinical Global Impression - Severity (CGI-S) score. Investigators could decrease the dosage to the original dosage at any time after the increase in dosage if there was an adverse event.

The overall study design is presented in Figure B.4.2.

Figure B.4.2:Overall study design (Study 99012)



a. All patients were dosed with 10mg/day at the start of the double-blind period. The dose could be increased to 20mg/day at Week 4, 6 or 8.

Rationale for study design:

A double-blind, placebo-controlled design is the 'gold standard' design for investigating the efficacy and safety profile of a compound for this type of indication. The treatment duration of 12 weeks was chosen since clinically and statistically significant improvements in SAD have been seen with other SSRIs within a 12-week treatment period[14 15 16].

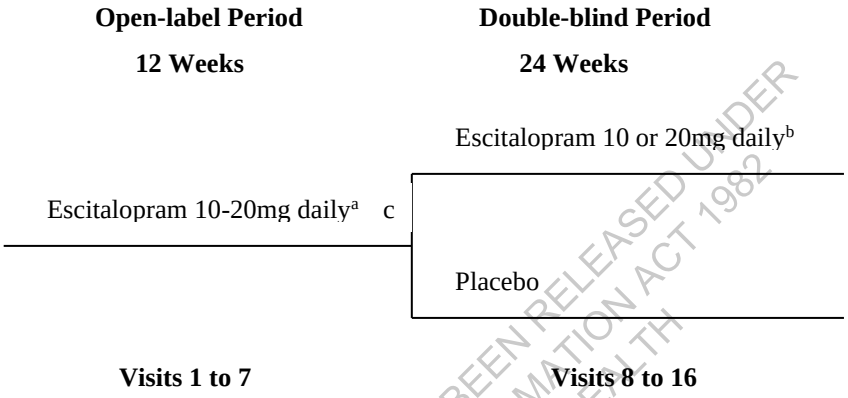
The dose of 10-20mg/day of escitalopram was chosen since it was expected that it would be equivalent to the dose range of 20-40mg/day of citalopram already shown to be effective in open-label studies of this disorder (consistent with the PBPA Therapeutic Relativities and the escitalopram Approved Product Information). A placebo run-in period allowed both the opportunity to exclude patients who respond to placebo therapy to be excluded and washout psychoactive medication which had been taken prior to screening and which may influence social behaviour. The one-week duration also provided time for assessment of laboratory test results and ECGs.

b) Study 99269

This multinational, multicentre study consisted of a 12-week open-label period with flexible doses of escitalopram doses and a 24-week randomised, double-blind, parallel-group, fixed dose comparison of escitalopram and placebo in the prevention

of relapse of SAD. Throughout the double-blind period the investigators evaluated relapse symptoms. Relapse was defined either as a Liebowitz Social Anxiety Scale (LSAS) total score ≥10 points greater than that at randomisation; or as withdrawal of the patient from the study due to unsatisfactory treatment response (lack of efficacy), as judged by the investigator. The overall study design is presented in Figure B.4.3.

Figure B.4.3:Overall study design (Study 99269)



a. All patients were dosed with 10mg/day at study start. The dose could be increased to 20mg/day at Week 2, 4 or 8.
b. The patients remained on the dose to which they responded during the open-label period.
c. Response was defined as a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale. Non-responders left the study.

Rationale for study design:

The open-label period was included to detect responders to escitalopram treatment. The duration of 12 weeks was chosen since clinically and statistically significant improvements in SAD have been seen within a 12-week period[14 15 16]. The double-blind, placebo-controlled design is widely accepted for examining relapse prevention. In addition, treatment of patients for a total of 9 months provides long-term tolerability and safety data.

Summary of the key aspects of the identified trials

While all three studies provide useful information on the overall efficacy of escitalopram, Study 99269 is a relapse prevention study and thus the design is markedly different to that of the other two studies. Therefore, while the study is considered a key study and provides important information on whether patients continue to respond to escitalopram therapy, the results of this study cannot be combined to give an overall assessment of effect (i.e. meta-analysed) with the other two studies. Full details of the meta-analysis undertaken are provided in Section B.5.3.

B.4.5 Subject characteristics

Subject characteristics in the treatments arms were generally similar, both within and across studies. The key subject characteristics are discussed below. TableB.4.5 presents the baseline characteristics of participants in the treatment arms in the three key direct randomised trials.

Age, Sex, Race

Patients' mean age in the different treatment groups in the 3 studies ranged from 36-39 years. SAD has an early age of onset, of around 15 years of age and is usually associated with a long a particularly prolonged duration prior to diagnosis and treatment with the prevalence of SAD tending to decline in the elderly[13]. Generally, there was a higher prevalence of SAD in females. From the literature review there was approximately a 1:5 to a 1:2 ratio or males to females (these figures vary from country to country: see Attachment 2). In Australia the prevalence of SAD was 3% for females and 2.4% for males.[17]

SAD onset

The age of SAD onset was consistent in all of the studies and treatment arms within studies, ranging from 15-18 years. This is also consistent with the age of onset generally reported[13]. SAD usually develops in adolescence, though it may be many years later that patients are formally diagnosed. As the mean patient age was 36-39

years in the studies, the mean duration of SAD was 19-20 years. The onset of SAD rarely occurs after the age of 25.[18]

Level of impairment at baseline

The mean LSAS total score ranged from 92 to 96. In study 99270 the baseline LSAS values in the escitalopram 10mg group was numerically similar, but statistically significantly lower (p=0.028) than in the placebo group. In the relapse prevention study (Study 99269), the patients' mean baseline LSAS score prior to them receiving 12 weeks of open-label escitalopram was similar to baseline values in the other studies. After 12 weeks of open-label escitalopram therapy (i.e. prior to being randomised to receive 24 weeks of either escitalopram or placebo) the patients' mean LSAS Total Score had significantly improved to around 42.

The LSAS was used to assess the level of impairment of patients at baseline and the efficacy of therapy with active treatment. The maximum possible score is 144 of the LSAS[19]. Patients with SAD generally score above 50 points, whilst normal volunteers score below 30 points. Scores between 50-70 may be considered moderate and are associated with distress while scores over 70, and particularly over 90, are considered severe and are associated with functional impairment. In the studies a score of greater than or equal to 82 on the LSAS is classified as severe SAD (LSAS>70 is considered severe), thus with a mean score of 92-96 points in the current studies the patients are classified as having severe SAD associated with functional impairment.

The baseline MADRS total score was used to ensure that patients met the exclusion criteria of MADRS>18. MADRS total scores were used to assess the level of depressive symptoms still present in the study population even though patients with major depressive disorder were excluded. Patients in all groups and studies demonstrated a low level of depressive symptoms at baseline, based on the MADRS. In studies 99270 and 99012 all patient groups had a mean score of <8. In Study 99269 the mean scores were <4, as patients had received 12 weeks of open-label escitalopram at baseline.

TableB.4.5: Baseline characteristics of participants in the direct randomised trials

99270	ESC 10mg	ESC 20mg	Placebo
Mean age (years)	37.2	37	37
Sex (% male)	42.5	47.1	48.8
Race (%):			
Caucasian	98.8	100	100
Black	0	0	0
Asian	0.6	0	0
Other	0.6	0	0
Mean BMI (kg/m²)	23.9	23.8	24.1
Mean age of SAD onset (years)	16.9	17.5	17.9
Mean duration of SAD (years)	20.3	19.5	19.2
Mean LSAS Total Score (SD)	92 (15)	94 (14)	96 (14)
Mean MADRS Total Score (SD)	6.84 (4.35)	7.31 (4.68)	7.56 (4.80)
99012	**ESC**	**Placebo**	
Mean age (years)	39	36	
Sex (% male)	55.8	53.1	
Race (%):			
Caucasian	90.6	91.5	
Black	3.9	3.4	
Asian	2.8	1.7	
Other	2.8	3.4	
Mean BMI (kg/m²)	25	25	
Mean age of SAD onset (years)	15[a]	15[a]	
Mean duration of SAD (years)	24[a]	21[a]	
Mean LSAS Total Score (SD)	96 (17)	95 (16)	
Mean MADRS Total Score (SD)	7.59 (4.48)	7.50 (4.37)	
99269	**ESC**	**Placebo**	
Mean age (years)	36.6[b]	38.3	
Sex (% male)	54.2	51.4	
Race (%):			
Caucasian	94.7	95	
Black	4.2	2.2	
Asian	0	0.6	
Other	1.1	2.2	
Mean BMI (kg/m²)	24.2	24.2	
Mean age of SAD onset (years)	17.2	17.9[c]	
Mean duration of SAD (years)	19.2	20.4	
Mean LSAS Total Score (SD)			
Baseline I -Prior to open-label phase	95 (16)	94 (14)	
Baseline II – Prior to randomised therapy			
	44 (21)	43 (20)	
Mean MADRS Total Score (SD)	3.21 (3.14)	3.34 (3.51)	

BMI = body mass index; NR = not reported
Study 99270 Study Report – Tables 11, 12, 15, 27 (FAS data) – Other data is for the "All patients treated" population (APTS).
Study 99012 Study Report – Tables 6, 7- All data is for the "All patients treated" population (APTS).
Study 99269 Study Report – Tables 13, 14, 15, 32, - All data is for the "Full analysis set" population (FAS), immediately prior to randomisation into the double-blind period (called Baseline II in the study report)

a. Data reported in the Kasper et al. publication4. In the Study Report (p. 54-55) the following information is provided: "At baseline, the two treatment groups were statistically significantly unbalanced with respect to duration of SAD (p=0.021). When adjusting for the covariate "duration of SAD" in the model (p=0.39), the statistically significant difference of escitalopram relative to placebo was slightly higher than in the primary analysis with an estimate of –7.8 points (p=0.003). No statistically significant interaction between duration of SAD and treatment was found at the 10% level of significance (p=0.20). No statistically significant interaction between treatment and age of SAD onset was found."
b. Reported as 36 years in the Montgomery et al.[10] publication, with the same range quoted as in the Study Report.
c. Reported as 17 years in the Montgomery et al.[10] publication

Source documents

Data provided in this section is taken from the Study Reports provided. Page and/or table references are provided under the tables or in text.

B.5 Outcome measures and analysis of the direct randomised trials

Summary

The methods of analysis of the primary and secondary study outcomes are fully presented. In studies 99270 and 99012 the primary outcome was mean change from baseline to study endpoint in the Liebowitz Social Anxiety Scale (LSAS). This outcome was analysed using analysis of covariance (ANCOVA). Study 99269 investigated the relapse of patients following successful escitalopram therapy, with time to relapse as the primary study outcome.

The LSAS is considered a gold standard, patient-relevant outcome in assessing the impact of therapy in SAD. s38 A change of (minus) 10 points on the LSAS has been suggested in the literature as showing a clinically relevant improvement.

Other patient-relevant outcomes such as changes in the Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression – Severity (CGI-S) scales, Sheehan Disability Scale (SDS) and adverse event information are also reported in the studies and in this submission.

Details of the meta-analyses undertaken for this submission are provided in this section and in Attachment 5. Two of the three key studies (Study 99270 and 99012) have been meta-analysed to give an overall treatment effect at Week 12. Due to significant differences in study design, the results of one study (Study 99269) cannot validly be meta-analysed with the other two and thus the results for this study are presented separately in Section B.6.

The primary and secondary outcomes for the three key studies are presented in Section B.5.1 and B.5.2. Full details of the analyses undertaken are provided, including the meta-analysis of two of the key trials. The clinical importance of the outcomes measured in the trials is reviewed.

B.5.1 Primary outcomes

The primary outcomes, methods of statistical analysis and information on the sample size calculations in the three randomised, controlled trials are presented in TableB.5.1 below.

TableB.5.1:Primary outcomes and statistical analyses in the key studies

Trial ID	Definition of primary outcome	Method of primary statistical analysis
99270	Change from Baseline to Week 12 (LOCF) in LSAS total score	A general linear model for ANCOVA adjusting for centres and baseline LSAS total score was applied. An overall treatment comparison was made; if the overall F-test proved significance at the 5% significance level, then pairwise tests for differences between each of the ESC groups and placebo were performed. The appropriateness of the final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups, and evaluating the potential influence of covariates. Adjustment of p-values in multiple testing (pairwise comparison) was carried out in the primary analysis and where appropriate in the secondary analyses using Fisher's Protected Least Significance Difference (LSD) multiple Comparison Procedure. **Sample size calculation:** A standardised effect size in the two relevant ESC arms (10mg, 20mg) of 0.292 and 0.375 points, respectively was used in the sample size calculations to provide 80% power to detect a significant difference in the primary outcome at a 5% level of significance. An estimate of the standard deviation of the change in LSAS total score was set to 24 based on a previous Lundbeck Study.
99012	Change from baseline to last assessment of the LSAS total score	The primary efficacy analysis was based on a general linear model for ANCOVA with factors for treatment group, collective centres and with baseline score as a covariate. The appropriateness of the final model was evaluated by inspection and analysis of residuals, by comparing variability between treatment groups, and evaluating the potential influence of covariates. **Sample size calculation:** A signal-to-noise ratio of 0.40 at a significance level of 5% was used in the sample calculation to provide 90% power to detect a significant different in mean change from baseline to final assessment of the LSAS total score between the ESC and placebo treatment groups. The signal-to-noise ratio is the treatment difference (mean change from baseline for ESC versus placebo) divided by the pooled standard deviation.
99269	Time to relapse[a] in the double-blind period of the study.	A log-rank test compared the time to relapse for the ESC and placebo groups. Actual treatment days were used in the analysis, which was supplemented with Kaplan-Meier plots. The appropriateness and robustness of the primary analysis was further studied by investigating a possible effect of collective centres, and of a collective centres by treatment interaction. This was done by applying stratified log-rank test, Cox's proportional hazard model, and accelerated failure time models. Analyses taking the interval censored nature of the survival times into account were performed using accelerated failure time models. **Sample size calculation:** A non-relapse withdrawal rate of 15% and a cumulative relapse rate at Week 24 of 30% for ESC and 55% for placebo was used in the sample size calculation to provide 90% power to demonstrate the difference in relapse rate between the ESC and placebo groups at a 5% level of significance.

ANCOVA = analysis of covariance, ESC = escitalopram, FAS = LOCF = last observation carried forward
Study 99270 – p. 39, 40, 41.
Study 99012 – p. 36, 37, 38
Study 99269 – p. 41, 42, 43
a. Relapse defined either as a LSAS total score ≥10 points greater than that at randomisation; or as withdrawal of the patient from the study due to unsatisfactory treatment response (lack of efficacy), as judged by the investigator.

B.5.2 Secondary outcomes

All secondary outcomes and the statistical analysis methods used in the three direct randomised, controlled trials are presented in Table B.5.2 below.

The results of secondary outcomes not considered patient-relevant are not presented in this submission. See Section B.5.3.3 for a full listing of patient-relevant secondary outcomes that are reported in Section B.6 in this submission (and meta-analysed if sufficient data is available).

A full list of secondary outcomes that are not considered patient-relevant is also provided in Section B.5.3.3. The results of all secondary outcomes are available in the individual Study Reports provided

TableB.5.2:Secondary outcomes and analyses in the key studies

Trial ID	Definition of secondary outcome	Method of statistical analysis
99270	• Change from baseline to each visit in LSAS total score • Proportion of patients with a ≥50% reduction in LSAS total score from baseline to visit • Change from baseline to last assessment in LSAS subscales (fear/ anxiety, avoidance) scores • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with a CGI-I score ≤2 per visit • Proportion of patients with a CGI-S score ≤2 per visit • Change from baseline to each visit in SDS items 1-3 score • Change from baseline to each visit in MADRS total score. • AEs in the ESC and placebo groups • DESS score	The LSAS total score per visit, the change from baseline to each visit in LSAS subscales (fear/ anxiety avoidance) score, CGI-S and SDS (family, social and work) scores were analysed by ANCOVA using the model described for the primary analysis and applying nominal visits. Adjustment of p-values in multiple testing (pairwise comparison) was carried out in the primary analysis and where appropriate in the secondary analyses using Fisher's Protected Least Significance Difference (LSD) multiple Comparison Procedure. In the secondary analyses, pairwise comparisons were only performed if the overall F-test was significant at the 5% level.
99012	• Change from baseline to each visit in LSAS total score • Change from baseline to last assessment in LSAS subscales (fear/ anxiety, avoidance) scores • Change from baseline to final assessment in LSAS single items • CGI-S score per visit • Change from baseline to each visit in CGI-S score • CGI-I score per visit • Proportion of patients with a CGI-I score ≤2 per visit • Change from baseline to each visit in SDS items 1-3 score • Change from baseline to each visit in MADRS total score • AEs in the ESC and placebo groups	Analyses of LSAS total scores were performed on OC, using repeated measures techniques to model and compare the treatment groups over all assessment points simultaneously. The LSAS total score per visit, the change from baseline to visit of the LSAS subscales (fear/ anxiety, avoidance) score and the SDS total score were analysed by ANCOVA (using the model described for the primary endpoint) and applying nominal visits. The CGI-S and CGI-I scores were analysed in the same way, however the final CGI-S and CGI-I scores were also analysed using the non-parametric Cochran-Mantel-Haenszel mean score statistic with modified ridit scores. Between group comparisons of the proportion of patients considered to be treatment responders were performed using Chi-squared and Fisher's exact tests for the CGI-I score ≤2 per visit
99269	• LSAS total score • Change from baseline(s) in the LSAS total score • LSAS avoidance and fear/anxiety subscale score • SDS items (work, social life and family life) • Change from baseline of the SDS items • CGI-S score • CGI-S change from baseline • CGI-I score in open-label period • Change from baseline to each visit in MADRS total score. • AEs in the ESC and placebo groups • DESS score	All secondary efficacy parameters were analysed by visit using ANCOVA (OC and LOCF) adjusting for study centre and baseline values.

ANCOVA = analysis of covariance
Source: Study 99270 – p. 41, 42; Study 99012 – p. 38, 39; Study 99269 – p.43, 44,

B.5.3 Analysis of the trial data

A large number of primary and secondary outcomes have been analysed in the three key studies. In addition, the results of patient-relevant outcomes have been meta-analysed as described in Section B.5.3.2. The primary and patient-relevant secondary outcomes have been meta-analysed (if sufficient data is available) and reported in this submission.

B.5.3.1 Analysis of the individual studies

The method of analysis of the primary and secondary outcomes of the three key studies has been provided in Section B.5.2. A large number of clinical outcomes were assessed. The clinical importance of these outcomes is discussed in Section B.5.4.

Study 99270 and 99269 both had 24-week (double-blind) active treatment periods, while Study 99012 had a 12-week active treatment period. Data is reported at study endpoint (Week 24) and at Week 12 (where available) for Study 99270 and 99269.

The Clinical Study Reports contain results for mean change from baseline for the continuous outcomes (e.g. LSAS, SDS Scores) as well as adjusted mean change from baseline (using ANCOVA) for the same outcome. As **adjusted** mean change was specified in the analysis for the primary and secondary outcomes, these results are reported in the individual study results in Section B.6. However the (unadjusted) change values are used for the meta-analysis. This leads to slight differences in the values reported for the individual studies and in the individual study meta-analysis data.

B.5.3.2 Meta-analyses undertaken

A meta-analysis combining the results of two of the key studies (Study 99270 and Study 99012) has been undertaken. See Attachment 5 for full details of study methodology and results. Some key issues in the design and conduct of the meta-analysis are highlighted below.

Excluded study (Study 99269)

Study 99269 has not been meta-analysed with the other two key studies. It is not possible to validly combine the results of the three direct comparative studies, due to significant differences in the objectives and design of Study 99269 compared with the other two key studies, leading to different patient populations being randomised to active treatment.

Study 99269 was a relapse prevention study. The trial was undertaken in order to determine the rate of patient relapse following successful treatment of SAD. All patients who met the eligibility criteria received open-label escitalopram for 12 weeks prior to study randomisation. Only patients who responded to therapy were randomised to continue in the relapse prevention study (since in order to be able to relapse, a patient must have responded to treatment). Thus the patients entering the randomised active treatment phase of this study were a "responder sub-population" of the patients with SAD who were initially eligible to enter the study. This is a different total patient population to that of Study 99270 and 99012. Due to the significant differences in the patient population randomised in Study 99269 (the relapse prevention study), compared with the other treatment studies, the results could not validly be combined in a meta-analysis.

Escitalopram treatment arms combined in the meta-analysis

Study 99270 was a fixed-dose study comparing three doses of escitalopram - 5mg, 10mg and 20mg daily – with placebo. Study 99012 was a flexible dose study with patients taking escitalopram 10mg to 20mg daily or placebo. Patients in this study took a mean daily dose of 17.1mg at Week 12. The meta-analysis combined the results of the fixed dose escitalopram 20mg daily treatment arm in Study 99270 with the flexible dose escitalopram arm in Study 99012, as these were the most similar study treatment arms that could be combined.

Treatment time-point analysed

Study 99012 had a 12 week active treatment phase. Study 99270 had a 24 week active treatment phase, with most outcomes also being reported after the first 12 weeks. The 12 week outcome data for each of the two studies was combined in the meta-analysis. This is important, as patients generally continued to improve from

weeks 12-24 in the two 24 week studies. Thus the results of the meta-analysis are likely to underestimate the true value of escitalopram therapy. Section B.6 for details of 12 and 24 week responses in Study 99270 and 99269.

B.5.3.3 Outcomes analysed in the meta-analysis and/or individual studies and reported in Section B.6

There are a large number of secondary outcomes reported in Study 99270 and Study 99012.TableB.5.3lists the outcomes that have been meta-analysed and/or reported in the individual studies with the results presented in Section B.6 of the submission.

TableB.5.3: Patient-relevant outcome results reported in Section B.6

Patient-relevant outcome	Trial ID			
	Meta-analysis (of Study 99270 & 99012)	Study 99270	Study 99012	Study 99269
Time-point analysed and reported[a]	**Week 12[b]**	**Week 12 & 24**	**Week 12**	**Week 12 & 24**
Primary outcome				
Change in mean LSAS Total Score	√	√	√	√[c]
Time to relapse	NA	NA	NA	√
Secondary efficacy outcomes				
Proportion of patients with a ≥50% reduction in LSAS score	NR	√	NR	NR
CGI-I Score	√	√	√	NR
Number and % patients with CGI-I≤2 (CGI-I responders)	√	√	√	NR
Change in mean CGI-S Score	√	√	√	√
Number and % patients with CGI-S≤2	NR	√	NR	NR
Change in SDS Work Scores	√	√	√	√
Change in SDS Social Scores	√	√	√	√
Change in SDS Family Scores	√	√	√	√
Change in MADRS total score	√	√	√	√
Secondary safety outcomes				
Total study withdrawals	√	√	√	√ Week 24 only
Study withdrawals - due to lack of efficacy	√	√	√	√ Week 24 only
Study withdrawals – due to AEs	√	√	√	√ Week 24 only
Patients with TEAEs	√	√	√	√ Week 24 only
TEAEs reported in ≥5% of patients	NR	NR	√	√ Week 24 only

Key:
√ = outcome reported in the Study Report or analysed in the meta-analysis and results presented in Section B.6
NA = not available – not a pre-defined study outcome, therefore data not collected
NR = not reported – data not reported for that outcome
Notes:
All change outcomes are change from baseline
a. Study 99012 had 12 weeks of randomised treatment. The other two studies had 24 weeks of randomised treatment. The meta-analysis was conducted using 12 week data (i.e. the longest timepoint available for both the analysed studies)
b. Data also reported at Week 4 and Week 8 for the primary outcome and CGI-responders (i.e. CGI-I≤2)
c. Change in mean LSAS Score was a secondary endpoint in Study 99012

TableB.5.4 lists the study outcomes reported in the individual studies that have not been meta-analysed or reported in Section B.6 for the reason stated.

TableB.5.4:Secondary outcome results that are not presented in Section B.6 (with reasons)

Secondary outcomes	Trial ID			Reason
	Study 99270	Study 99012	Study 99269	
Change from baseline to each visit in LSAS Score	√	√		Change from baseline to Week 12 and Week 24 (i.e. study mid and/or endpoint) results reported, rather than per visit
Proportion of patients with a ≥50% reduction in LSAS score at each visit	√			
CGI-I Score per visit	√	√		
Number and % patients with CGI-I≤2 at each visit	√	√		
CGI-S Score per visit	√	√	√	
Number and % patients with CGI-S≤2 at each visit	√			
Change from baseline to each visit in MADRS Score	√	√	√	
Change in CGI-S score per visit	√	√	√	
Change from baseline to last assessment in LSAS single items	√		√	Total Score results reported. Subscale results are difficult to interpret meaningfully.
Change in mean LSAS Avoidance Sub-scale Score	√	√	√	
Change in mean LSAS Fear/Anxiety Sub-scale Score	√	√	√	
Change in LSAS single items	√	√		
CGI-I score in open-label period			√	Randomised, double-blind phase results reported
Total adverse events	√	√	√	Treatment-emergent AEs and AEs leading to withdrawal reported
DESS score	√		√	Looks at discontinuation effects after completion of active treatment

Key:
√ = results for this outcome available in the Study Report, however the results are not presented in Section B.6 for the reasons provided

B.5.4 Clinical importance of the outcomes used in the studies

Liebowitz Social Anxiety Scale (LSAS)

Change in mean LSAS Total Score is the primary outcome in Study 99270 and 99012. While a variety of measurement scales have been developed to quantify the severity of SAD, the most widely used scale is the LSAS. It has been able to establish efficacy in a large number of placebo-controlled studies in SAD and is currently viewed as the gold standard[13]. s38

An improvement of 10 points on the LSAS has been suggested as showing a clinically relevant improvement[13]. This is also in line with the clinically relevant difference between drug and placebo for licensing approval.[20]

Clinical Global Impression– Improvement (CGI-I)

CGI-I score results are secondary study outcomes in the studies. The CGI-I scale has been used to identify responders to therapy, specifically patients reporting a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale have been defined as responding to therapy. While this global scale is not recommended as a primary scale, it may be useful as a secondary scale to help judge the clinical relevance of the finding[13]. This was consistent with the pre-specified magnitude identified in the trials.

B.5.5 Measurement scales used as primary and secondary outcomes in the studies

Liebowitz Social Anxiety Scale (LSAS)

The LSAS[21] is designed to assess SAD through evaluation of fear and avoidance. The LSAS is a clinician-administered (interview) scale to evaluate the wide range of social situations within the last 7 days that are typically difficult for individuals with

SAD. The LSAS includes 24 items: 13 describe performance situations and 11 describe social interaction situations. Each item is rated with respect to fear (0 to 3 = *none, mild, moderate, severe,* respectively) and avoidance (0 to 3 = *never, occasionally, often, usually,* respectively). Thus, the LSAS provides an overall social anxiety severity rating, and additionally scores four subscales: performance fear, performance avoidance, social fear, and social avoidance. Total scores for fear and avoidance as well as total LSAS scores are obtained by adding the scores.

The ratings are based upon an interview with the patient and were conducted by the same person at each visit, whenever possible. Only persons accepted by the study sponsor and trained as raters during a co-rating session were allowed to rate patients on the LSAS. The rater sessions were undertaken to increase inter-rater reliability, and were chaired by an experienced rater(s). At these sessions, video tapes were shown of patients with SAD; these patients were rated and the ratings discussed.

The maximum possible score is 144 of the LSAS[19]. Patients with SAD generally score above 50 points, whilst normal volunteers score below 30 points. Scores between 50-70 may be considered moderate and are associated with distress while scores over 70, and particularly over 90, are considered severe and are associated with functional impairment.[13,19]

As mentioned earlier, an improvement of 10 points on the LSAS has been suggested as showing a clinically relevant improvement[13]. However this should not be viewed in isolation and proportion of patients responding and importantly remitting should be considered to be at the very least of equivalent importance.

Responders[13]: LSAS: ≥35-50% reduction in score from baseline. Defining responders, as having a reduction in the initial score on the severity scale of 50%, used in other psychiatric conditions and which seems reasonable, has been reported to be useful in some studies in SAD. However, SAD tends to respond more slowly than the conditions where the 50% criterion has proved most useful. The studies indicate that at 12 weeks a 35% reduction in initial severity appears to be a useful measure with approximately half the patients achieving this criterion. This closely corresponds

to 31% reduction, which was determined from a study looking at the correlation between outcomes from the analysis of various trials (shown below).[13]

Remission[22]: Keeping in mind that some controversy may exist regarding remission standards for CGI, an analysis of remission for various trials found the following correlations between the various scales.

CGI Defined	Corresponding Reductions	
	MDRS	LSAS
Response CGI-I ≥50% reduction	39%	31%
Remission CGI-S ≤2	11 points	36 points

Given that a normal volunteers scores below 30 points on the LSAS the remission score suggested is not unreasonable. Indeed, consensus conferences addressing this issue have also arrived at remission being defined as LSAS≤30.[23 24]

Therefore in totality the results should be based on more than a change in score of ≥ 10 points and the totality of the evidence should be considered.

Clinical Global Impression (CGI)

The CGI[25] are categorical scales used as both primary (though they are not recommended as primary and are most useful as secondary scales to help judge the clinical relevance of the finding) and secondary efficacy scales and as categorical scales to define responders.[13] CGI consists of two subscales:

- Clinical Global Impressions – Improvement scale (CGI-I):
  This scale evaluates a patients' total improvement from baseline on a 7 point-scale, regardless of whether the improvement is related to the study product. The assessor rates the patient from 1 (*very much improved)* to 7 (*very much worse)*
- Clinical Global Impressions – Severity scale (CGI-S):
  This scale evaluates a patient's severity of disease on a 7-point scale based on the investigators total clinical experience with this population. The assessor

rates the patient from 1 (*normal, not at all ill*) to 7 (*among the most extremely ill patients*).

Responders and Remitters on the CGI scale are classified as:

Responders: CGI-I≤ 2 (much or very much improved)[13] or CGI-I ≥50% reduction[22]. These patients have improved but have not yet reached remission.

Remission:[13] CGI-S≤ 2 (normal, not at all ill, or borderline illness)..

Sheehan Disability Scale (SDS)

The SDS[26] is a 3-item scale to measure impairment. The items address the impact of symptoms of SAD on work, social life, and family life, within the last 7 days. The rating is based up an interview with the patient. This scale has proved robust in most studies and provides evidence of an improvement is disability in almost all studies where it is used.[13] The SDS has been able to distinguish an effective treatment from placebo, both in the short and long-term studies. Conclusions arrived at consensus conferences identify remission at SDS≤1 on each item (mildly disabled).[23 24]

Montgomery and Åsberg Depression Rating Scale (MADRS)

The MADRS[27] consists of 10 items, each rated on a scale from 0 (*no symptoms*) to 6 (*severe symptoms*). All the items are core symptoms of a depressive episode and thus measure the severity of a depressive episode for the previous 7 days.

The symptoms rated are: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.

The MADRS is based on a clinical interview with the patient beginning with general questions about symptoms and gradually becoming more detailed to allow for a precise rating of depression severity.

Source documents

All study data provided in Section B.5 comes from the Study Reports provided (Study 99270, 99012 and 99269). Page and/or table references are provided under the tables or in text. .

B.6 Systematic overview of the results of the direct randomised trials

Summary

The results of the randomised, controlled, double-blind studies demonstrate that escitalopram treatment significantly reduces the severity of Social Anxiety Disorder, compared with placebo and improved patient functioning. s38

Mean improvement in LSAS Total Score was the primary study outcome in the two treatment studies and a key secondary outcome in the relapse-prevention study. In all studies escitalopram significantly improved the mean LSAS total score compared with placebo. In addition, the percentage of patients defined as responders (based on both the LSAS and CGI-I scales) and remitters (based on the CGI-S scale) were significantly greater with escitalopram. The improvements seen were both statistically significant and clinically meaningful, demonstrating the clear benefit of escitalopram to this severely incapacitated patient group.

Figure B.6.1 depicts the timelines for the various trials. It outlines the level of information provided over a 36 week trial program for patients being treated with SAD. It clearly depicts, together with Table B.6.1 that there is a clinically superior effect with escitalopram.

. As can be seen a statistically different outcomes is observed in the primary and secondary outcomes. These differences are determined to be clinically relevant, as will be shown in the following sections.

Figure B.6.1: Clinical trials for SAD

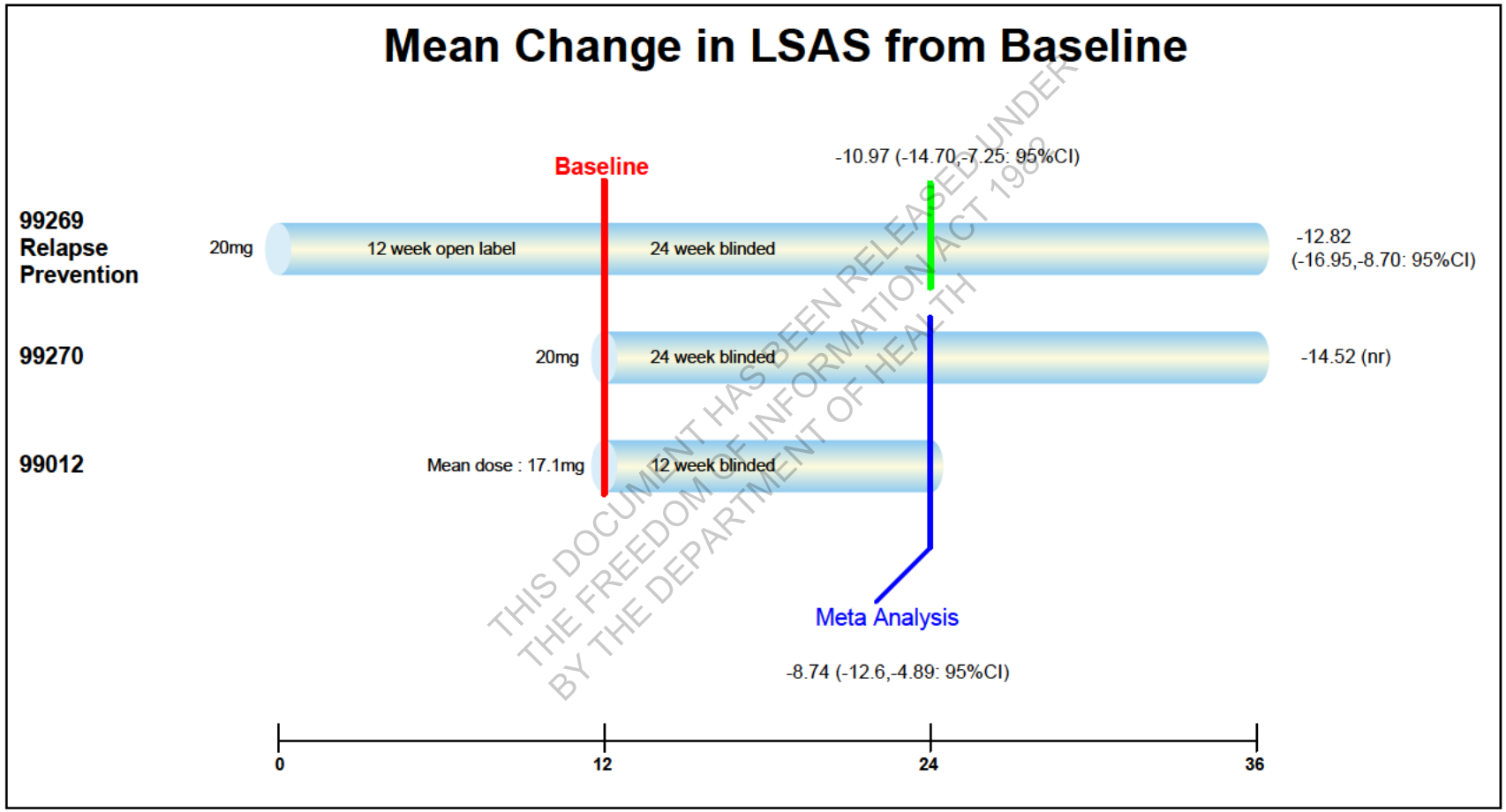


Table B.6.1: Summary results of primary outcome and meta-analysis

		99270			99012		99269 Relpase Prevention	
		Escitalopram 10mg	Escitalopram 20mg	Placebo	Escitalopram $\bar{x}$=17.1mg	Placebo	Escitalopram	Placebo
	n reporting data / N (%)	164/168 (98)	163/170 (96)	165/166 (99)	177/181 (98)	176/177 (99)	189/190 (99.5)	179/181 (99)
Unadjusted	**Mean LSAS total score (SD) at:**							
	Open Label	[redacted]					94.24 (15.72)	93.88 (14.09)
	Baseline	92.38 (14.93)	93.98 (13.99)	96.00 (14.46)	96.32 (17.35)	95.44 (16.35)	44.28 (20.84)	43.16 (19.94)
	Week 12	59.36 (26.81)	55.35 (28.76)	67.44 (26.81)	62.25 (30.67)	68.82 (29.70)	37.95 (22.41)	48.80 (26.53)
	Week 24 (endpoint)	52.57 (29.12)	46.17 (31.55)	62.72 (30.16)	[redacted]		35.71 (24.27)	48.50 (26.87)
	Mean change LSAS from baseline (SD) at:							
	Week 12	-33.02 (24.19	-38.63 (27.56)	-28.56 (22.84)	-34.07 (25.81)	-26.62 (26.09)	-6.20 (16.43)	5.54 (19.81)
	Week 24	-39.80 (28.31)	-47.80 (30.78)	-33.28 (26.55)	[redacted]		-8.43 (19.08)	5.24 (21.27)
	Difference of mean changes (95% CI), escitalopram versus placebo: Results from Meta-analysis at 12 weeks	[redacted]	-8.74 (-12.60, -4.89)				[redacted]	
	Difference of mean changes (95% CI), escitalopram versus placebo at 24 weeks	-6.92 (n.r.)	-14.52 (n.r)	[redacted]				
Adjusted	**Adjusted* mean change LSAS from baseline (SE) at:**							
	Week 12	-34.55 (1.96)	-39.79 (1.97)	-29.48 (1.95)	-34.45	-27.16	-6.13 (1.56)	4.85 (1.65)
	Week 24	-41.50 (2.17)	-49.13 (2.13)	-34.04 (2.17)	[redacted]		-8.28 (1.73)	4.55 (1.82
	Difference of adjusted* mean change LSAS (95% CI) - escitalopram versus placebo:							
	Week 12	-5.07 (-10.32, 0.18)	-10.31 (-15.56, -5.06)	[redacted]	7.29 (-12.37, -2.21)	[redacted]	-10.97 (-14.70, -7.25)	[redacted]
	Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25))	[redacted]	[redacted]		-12.82 (-16.95, -8.70)	[redacted]

Full details of the results of the included studies are provided in this section and in Attachment 6. The results are presented in the following sub-sections:

B.6.1 Primary outcome result – Change in mean LSAS Total Score

- For Study 99270 and 99012, presented individually
- Meta-analysis of Study 99270 and 99012 (at Week 12)

B.6.2 Results of the primary outcome for Study 99269 – relapse-prevention study

B.6.3 Results of key secondary efficacy results for the individual studies (provided in full in Attachment 6)

B.6.4 Results of the meta-analysis of key secondary outcomes (Study 99270 and 99012) at Week 12

B.6.5 Results of key secondary safety results for the individual studies (provided in full in Attachment 6)

B.6.6 Summary of efficacy and safety data

Change in mean LSAS total score is the primary outcome for Study 99270 and 99269.

s47E(d) This is followed by the primary outcome results of the relapse-prevention study (time to relapse). The results of the meta-analysis of the key secondary outcomes are presented next. Individual study key secondary efficacy and safety results are then presented, with full details available in Attachment 6.

The results of Study 99270 and 99012 demonstrate the efficacy and safety of escitalopram in the treatment of SAD. The results of the relapse prevention study

(Study 99269) demonstrate the continued efficacy and safety of escitalopram treatment in patients who have been initially successfully treated with escitalopram.

All results are sourced from the Clinical Study Reports, with Table and page references provided. Copies of the Clinical Study Reports have been provided with the submission.

B.6.1 Primary outcome – Mean change in LSAS Total Score

The primary outcome in Study 99270 and 99012 was mean change in LSAS Total Score. The results are presented individually for each study. s38 This is followed by the results of the meta-analysis of this outcome for Study 99270 and 99012 at Week 12.

B.6.1.1 Study 99270, Study 99012 and Study 99269 (Mean change in LSAS Total Score)

Study 99270 had a 24-week active treatment period. Data is reported at Week 12 and 24 to allow comparison with Study 99012 which was of 12 weeks duration (see Table B.6.2). Both mean change and adjusted mean change data is reported, as adjustment using ANOVA was the pre-specified method of analysis in the individual studies, with adjustment leading to only very small differences in the adjusted versus unadjusted results.

Table B.6.2: Results of primary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99270

Outcome Time point	Escitalopram 10mg	Escitalopram 20mg	Placebo	Source (Study Report)
n reporting data / N (%)	164/168 (98)	163/170 (96)	165/166 (99)	Table 27
Mean LSAS total score (SD) at:				
Baseline	92.38 (14.93)	93.98 (13.99)	96.00 (14.46)	
Week 12	59.36 (26.81)	55.35 (28.76)	67.44 (26.81)	
Week 24 (endpoint)	52.57 (29.12)	46.17 (31.55)	62.72 (30.16)	
Mean change from baseline (SD) at:				Table 29
Week 12	-33.02 (24.19	-38.63 (27.56)	-28.56 (22.84)	
Week 24	-39.80 (28.31)	-47.80 (30.78)	-33.28 (26.55)	
Adjusted* mean change from baseline (SE) at:				Table 32
Week 12	-34.55 (1.96)	-39.79 (1.97)	-29.48 (1.95)	
Week 24	-41.50 (2.17)	-49.13 (2.13)	-34.04 (2.17)	
Difference of adjusted* mean changes (95% CI) - escitalopram versus placebo:				
Week 12	-5.07 (-10.32, 0.18)	-10.31 (-15.56, -5.06)		
Week 24	-7.45 (-13.29, -1.62)	-15.09 (-20.92, -9.25))		

SE = Standard error (least squares estimate)
* Using ANCOVA

The difference of the adjusted mean change in LSAS total score at Week 24 was –7.45 (95% CI –13.29, -1.62) in the escitalopram 10mg group and –15.09 (95% CI –20.92, -9.25) in the escitalopram 20mg group, both compared with placebo. The improvement in LSAS score was statistically significant for escitalopram 20mg at Week 12. The benefit of escitalopram continued to increase over time, and by Week 24 achieved statistical significance in both escitalopram groups.

The final (i.e. 12 week) primary outcome results for Study 99012 are presented in TableB.6.3 below.

TableB.6.3:Results of primary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99012

Outcome Time point	Escitalopram[a]	Placebo	Source (Study Report)
n reporting data / N (%)	177/181 (98)	176/177 (99)	Table 18
Mean LSAS total score (SD):			
Baseline	96.32 (17.35)	95.44 (16.35)	
Week 12	62.25 (30.67)	68.82 (29.70)	
Mean change from baseline (SD) at:			Table 20
Week 12	-34.07 (25.81)	-26.62 (26.09)	
Adjusted[b] mean change from baseline[c] at:			Table 23
Week 12	-34.45	-27.16	
Difference of adjusted[b] mean change (95% CI) - escitalopram versus placebo:			
Week 12	-7.29 (-12.37, -2.21)		

SE = Standard error (least squares estimate)
a. Flexible dose study, mean escitalopram study dose at Week 12 was 17.1mg daily
b. using ANCOVA
c. SD/SE values not reported

At the end of the 12 week study period, escitalopram provided a significant improvement in the primary study outcome, compared with placebo.

Study 99269 was a 24-week randomised, double-blind, relapse prevention study. Prior to randomisation all patients received open-label escitalopram for 12 weeks. Patients that responded to therapy were then randomised into the double-blind, active treatment phase of the study. While time to relapse was the primary study outcome, a secondary outcome of importance was the improvement in LSAS total score. These results are presented in TableB.6.4 below.

TableB.6.4:Results of secondary outcome (Adjusted mean change in LSAS total score, LOCF) – Study 99269

Outcome Time point	Escitalopram[a]	Placebo	Source (Study Report)
n reporting data / N (%)	189/190 (99.5)	179/181 (99)	
Mean LSAS total score (SD):			
Open-label phase Baseline	95.11 (15.65) (n=190)	96.24 (14.35) (n=181)	Table 32
Baseline (prior to randomisation)	44.28 (20.84)	43.16 (19.94)	Table 61
Week 12	37.95 (22.41)	48.80 (26.53)	
Week 24	35.71 (24.27)	48.50 (26.87)	
Mean change from baseline (SD) at:			
Week 12	-6.20 (16.43)	5.54 (19.81)	Table 63
Week 24	-8.43 (19.08)	5.24 (21.27)	
Adjusted mean change from baseline (SE) at:			
Week 12	-6.13 (1.56)	4.85 (1.65)	
Week 24	-8.28 (1.73)	4.55 (1.82	Table 65
Difference of adjusted[b] mean change (95% CI) -- escitalopram versus placebo:			
Week 12	-10.97 (-14.70, -7.25)		
Week 24	-12.82 (-16.95, -8.70)		

SE = Standard error (least squares estimate)
a. Flexible dose study, mean escitalopram study dose was 17.3mg daily
b. using ANCOVA

Patients in the relapse-prevention study had lower (i.e. improved) LSAS total Scores at baseline compared with those in the two treatment studies (Study 99270 and 99012) as they had received 12 weeks of open-label therapy with escitalopram. Prior to the 12 weeks open-label escitalopram therapy, the patients' baseline LSAS scores were similar to the baseline scores seen in the treatment studies (Study 99270 and 99012)

At Week 12 and 24 after randomisation to escitalopram or placebo, patients in the escitalopram group had an improvement in mean LSAS Total Score compared with patients receiving placebo. Patients had a difference in the adjusted mean change of –10.97 (95% CI –14.70 to –7.25) at Week 12, compared with placebo. Further improvement occurred at Week 24 with a difference of –12.82 (95% CI –16.95 to –8.70) between escitalopram therapy and placebo. This difference was both statistically significant and clinically meaningful, with both point estimates exceeding the clinically important difference of –10 (see Section B.5.4 for details).

Of note, patients continued to improve from the time they received open-label escitalopram until the final assessment at Week 24, after a total of 36 weeks of escitalopram therapy.

B.6.1.2 Meta-analysis

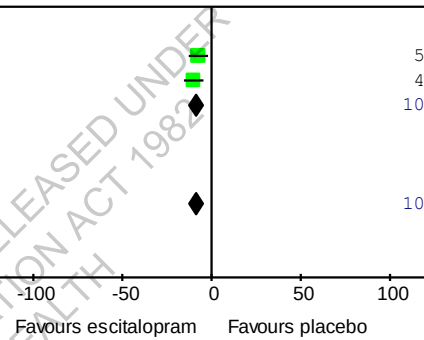
The meta-analysis combines the primary outcome results for Study 99270 and 99012 (**using the unadjusted change data**) at Week 4, 8 and 12. The data utilised for 99270 was 20mg arm of escitalopram patients, given that the mean dose for 99012 was 17.1mg. The data is presented below with full details of the study methodology available in Attachment 5. As Study 99012 was only of 12 weeks duration, the longest time-point that could be meta-analysed was 12 weeks. The results of Study 99270 (and Study 99269) demonstrate that patients receiving escitalopram continue to improve during Week 12 to Week 24 of therapy. Therefore the results of the meta-analysis underestimate the true value of escitalopram therapy, i.e. that occurring beyond 12 weeks of therapy. The results of Study 99269 could not be meta-analysed with the other two studies due to significant differences in study design, leading to differing patient populations.

The results of the meta-analysis were conducted for the duration of 4, 8 and 12 weeks. Only the 12 week data is presented here, all results are presented in Attachment 5. The 12 week data is presented in Figure B.6.2.

Figure B.6.2:Results of primary outcome (mean change in LSAS total score, LOCF) at Week 12 – meta-analysis of Study 99270 and 99012

Review: Escitalopram (Lexapro) - SAD
Comparison: 01 Change in Mean LSAS Total Score (FAS LOCF) - primary endpoint
Outcome: 03 Change in Mean LSAS Total Score (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
99012	177	-34.07(25.81)	176	-26.62(26.09)		50.62	-7.45 [-12.86, -2.04]
99270	163	-38.63(27.56)	165	-28.56(22.84)		49.38	-10.07 [-15.55, -4.59]
Subtotal (95% CI)	340		341			100.00	-8.74 [-12.60, -4.89]
Test for heterogeneity: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%							
Test for overall effect: Z = 4.45 (P < 0 00001)							
Total (95% CI)	340		341			100.00	-8.74 [-12.60, -4.89]
Test for heterogeneity: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%							
Test for overall effect: Z = 4.45 (P < 0 00001)							



Source: Meta-analysis Report - Attachment 5

The weighted mean change in the LSAS total score continued to increase from Week 4 to Week 12. At Week 12 the difference in the weighted mean change was -8.74 (95% CI -12.60, -4.89). This is a statistically significant improvement in LSAS total score in the escitalopram group, compared with placebo. Importantly, the 95% confidence intervals include the value 10, the clinically important improvement in LSAS Total Score described in Section B.5.4. Based on the results of the 24 week treatment and relapse-prevention studies, it would be expected that escitalopram treated patients would continue to improve beyond the 12 week meta-analysis period reported.

B.6.2 Relapse-prevention Study 99269 - primary outcome result (time to relapse)

Study 99269 was a relapse prevention study. All patients received 12 weeks of open-label escitalopram, with responders then randomised to receive 24 weeks of escitalopram or placebo. The primary study outcome was time to relapse. The results are presented in TableB.6.5 and graphically in Figure B.6.3.

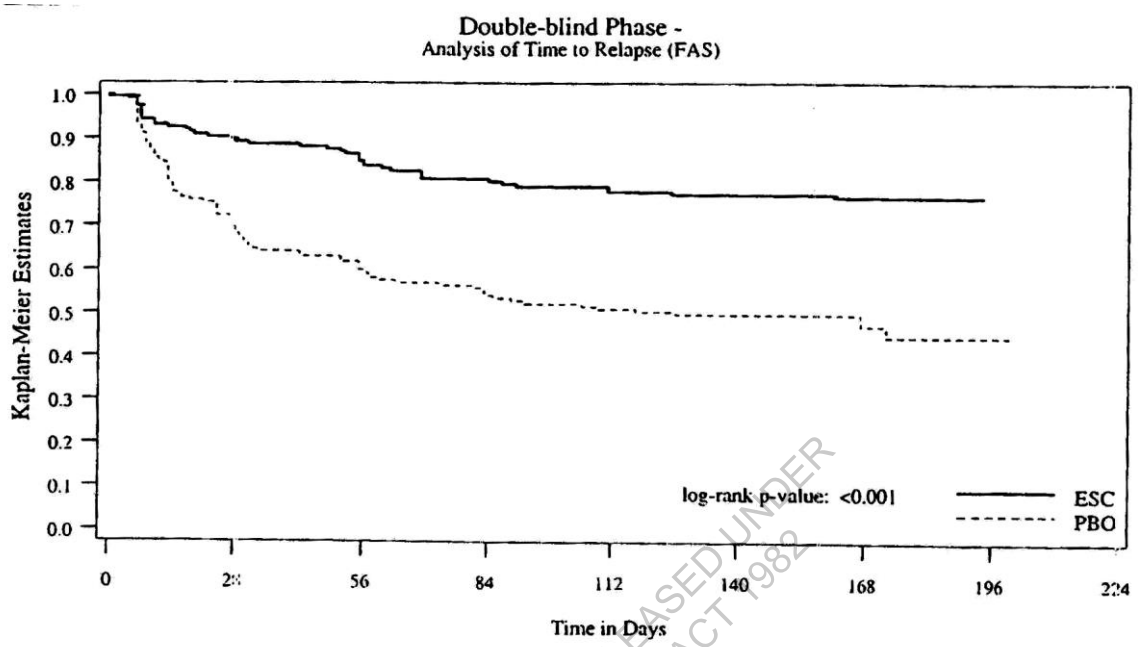
Due to the relatively few relapses in the escitalopram group, median survival times could not be estimated satisfactorily. Instead descriptive mean survival times have been presented.

TableB.6.5: Analysis of time to relapse (Study 99269)

Treatment	n / N (%)	No. of relapses	% Relapsed	Mean survival days
Escitalopram Placebo	190/190 (100) 181/182 (99.5)	42 91	22.1 50.3	135.3 103.5
Log-rank P value	**Hazard Ratio (Cox)**	**Standard Error**	**Cox-Model P-value**	
5.0E-09	2.83 (NR)	1.21	2.7E-08	

Source – Table 42
NR.: not reported

Figure B.6.3: Analysis of time to relapse (Study 99269)



The results of the primary analysis show a clear beneficial effect of escitalopram relative to placebo, with more than twice as many patients in the placebo group relapsing. (Hazard Ratio 2.83, log rank test, p<0.001). This study demonstrates the benefit of escitalopram in reducing the risk of relapse once patients have responded to therapy.

B.6.3:Secondary outcome results for the individual studies - efficacy

The key secondary efficacy results are summarised in this section and presented for the individual studies in full in Attachment 6. A summary list of these efficacy outcomes and the studies in which they are available is presented in TableB.6.6 below.

TableB.6.6: Key secondary efficacy results for the individual studies presented in Attachment 6

	Study 99270	Study 99012	Study 99269
Time-point analysed and reported[a]	**Week 12 & 24**	**Week 12**	**Week 12 & 24**
Secondary efficacy outcomes			
Proportion of patients with a ≥50% reduction in LSAS score	√	NR	NR
CGI-I Score	√	√	NA
Number and % patients with CGI-I≤2 (CGI-I responders)	√	√	NA
Change in mean CGI-S Score	√	√	√
Number and % patients with CGI-S≤2	√	NR	NR
Change in SDS Work Scores	√	√	√
Change in SDS Social Scores	√	√	√
Change in SDS Family Scores	√	√	√
Change in MADRS total score	√	√	√

Key:
√ = outcome reported in the Study Report and results presented in Section B.6.4
NA = not available – not a pre-defined study outcome, therefore data not collected
NR = not reported – data not reported for that outcome
CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; ESC = escitalopram, LSAS = Liebowitz Social Anxiety Scale, MADRS = Montgomery and Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale.
Notes:
a. All change outcomes are change from baseline

Summary of key secondary efficacy outcome results

Studies 99270 and 99269 were both of 24 weeks duration (randomised, double-blind phase) Results of the secondary efficacy outcomes demonstrate that patients continue to gain benefit from escitalopram beyond 12 weeks and up to at least 24 weeks of therapy. Patients on escitalopram showed a significantly greater response to therapy (based on significant improvements in % patients with a ≥50% reduction in LSAS, CGI-I scores, % patients with CGI-I≤2 and CGI-S scores). Measures of functional impairment (SDS) also showed benefits with escitalopram therapy.

Study 99270 also compared two different daily doses of escitalopram (10mg and 20mg) over 24 weeks of therapy. The benefits of therapy were greater with escitalopram 20mg daily in all the efficacy outcomes, compared with escitalopram 10mg daily.

The results of the key secondary outcomes measures that are markers of disease severity and improvement with therapy (i.e. % patients with ≥50% improvement in LSAS Score, CGI-I Score and % patients with a CGI-I or CGI-S Score ≤2) are presented for Study 99270 and Study 99012 in TableB.6.7 below. In all cases escitalopram significantly improved patient outcomes.

The Sheehan Disability Scales (SDS) scores (Work, Social and Family) were also statistically significantly improved in Study 99270 at Weeks 12 and 24. At Week 12 in Study 99012 there were statistically significant improvements in SDS Work and Social Scores, with a trend towards improvement in the Family Score. The SDS is a measure of functional disability in SAD in the three key affected areas.

TableB.6.7: Summary results of secondary efficacy outcomes – Study 99270 and Study 99012 (% patients with ≥50% reduction in LSAS, Clinical Global Impression – Improvement, % patients with CGI-I and CGI-S≤2)

	Study 99270		Study 99012
Outcome	**Escitalopram 10mg**	**Escitalopram 20mg**	
% of patients with ≥50% reduction in LSAS total score			
Mean % difference (95% CI) esc vs placebo			NR
Week 12	8.7 (-0.6, 18.0)	18.7 (8.9, 28.4)	
Week 24:	17.2 (7.0, 27.5)	27.3 (17.1, 37.6)	
Relative Risk* (95% CI) esc vs placebo at:			NR
Week 12	1.42 (0.97, 2.08)	1.91 (1.34, 2.72)	
Week 24	1.61 (1.20, 2.15)	1.96 (1.49, 2.59)	
NNT* (95% CI) vs placebo at:			NR
Week 12	11 (6, 167)	5 (4, 11)	
Week 24	6 (4, 14)	4 (3, 6)	
CGI-I[a]			
Difference of adjusted mean CGI-I Score esc vs placebo (95% CI) at:			
Week 12	-0.21 (-0.43, 0.01)	-0.32 (-0.55, -0.10)	-0.37 (-0.59, -0.16)
Week 24	-0.21 (-0.45, 0.02)	-0.48 (-0.72, -0.25)	-
% Patients with CGI-I ≤2			
Difference in % patients with CGI-I ≤2 esc vs placebo (95% CI) at:			
Week 12	13.7 (3.0, 24.4)	20.8 (10.2, 31.3)	15.6 (5.3, 25.9)
Week 24	7.6 (-3.1, 18.4)	19.6 (9.3, 30.0)	-
Relative Risk* (95% CI) esc vs placebo at:			
Week 12	1.33 (1.06, 1.67)	1.50 (1.21, 1.87)	1.40 (1.12, 1.77)
Week 24	1.15 (0.94, 1.41)	1.39 (1.16, 1.67)	-
NNT* (95% CI) esc vs placebo at:			
Week 12	7 (4, 33)	5 (3, 10)	6 (4, 19)
Week 24	13 (5, 32)	5 (3, 11)	-
Patients with CGI-S≤2			
Difference in % patients with CGI-S ≤2 esc vs placebo (95% CI) at:			NR
Week 12	11.1 (2.7. 19.4)	13.7 (5.1, 22.2)	
Week 24	17.8 (8.3, 27.3)	26.6 (16.9, 36.4)	
Relative Risk* (95% CI) esc vs placebo at:			NR
Week 12	1.83 (1.14, 2.94)	2.03 (1.27, 3.22)	
Week 24	1.92 (1.33, 2.77)	2.37 (1.67, 3.38)	

	Study 99270		Study 99012
Outcome	Escitalopram 10mg	Escitalopram 20mg	
NNT* (95% CI) esc vs placebo at:			NR
Week 12	9 (5, 37)	7 (5, 20)	
Week 24	6 (4, 12)	4 (3, 6)	

CGI-I = Clinical Global Impression – Improvement, CGI-S= Clinical Global Impression – Severity, esc = escitalopram, LSAS = Liebowitz Social Anxiety Scale, NR = not reported
* calculated value

The key secondary efficacy outcomes for the relapse-prevention Study 99269 are presented in full in Attachment 6. The proportion of patients with ≥50% reduction in LSAS Total Score was not reported, while CGI-I was not measured in this study. There was a statistically significant improvement in CGI-S total score and in all the SDS scores (Work, Social, Family) at both Weeks 12 and 24 in Study 99269.

B.6.3 Meta-analysis of key secondary outcomes

Revman format results for the meta-analysis of the key secondary outcomes of the treatment studies (Study 99270 and 99012) are presented in Figure B.6.4 to Figure B.6.14 below. Results are presented at 12 weeks, with CGI-I ≤2 (sometimes called CGI-I responders) 12 weeks. The meta-analysis presented in Attachment 5 also contains results reported at 4 and 8 weeks.

It is important to note that Study 99270 was of 24 weeks duration, so the meta-analysed results do not reflect the value of escitalopram during the second 12 weeks of study treatment. In addition, due to differences in study design the relapse-prevention study (Study 99269) could not be validly meta-analysed with the other two treatment studies. Study 99269 also provides data on the use of escitalopram for 24 weeks, rather than the 12 weeks reported in the meta-analysis. See Section B.6.4 for the 24 week study results.

Summary of meta-analysis results

Results for the meta-analysis are reported in Figure B.6.4 to Figure B.6.14. Escitalopram was statistically significantly superior to placebo for all efficacy outcomes relating to reduced severity of SAD at Week 12 (CGI-I Score, % patients

with CGI≤2 also called 'remitters', CGI-S). The percentage of patients with CGI-I≤2 (or CGI-I 'responders', patients who are rated as 'very much or 'much' improved on the CGI-I scale) was 50% greater with escitalopram at 12 weeks (RR 1.46; 95% CI 1.24, 1.71). Two functional disability measures on the Sheehan Disability Scale (SDS) – work and social scores - also showed a statistically significant benefit for escitalopram, with the exception being the SDS Family score (where there was a trend towards significance).

The MADRS score was not an efficacy endpoint, but rather an assessment of depressive status. While escitalopram was superior to placebo at week 12, the MADRS score seen throughout the studies in all treatment groups was below the recognised cut-off for a depressive episode (i.e. <8), indicating that benefits seen with escitalopram were due to treatment of SAD, rather than co-morbid depression.

Patients receiving escitalopram had a higher rate of treatment-emergent adverse events than placebo and more adverse events leading to withdrawal, as would be expected of an active treatment compared with placebo. However with escitalopram there was a significant 62% reduction in patients withdrawing from the studies due to lack of efficacy (RR 0.38, 95% CI 0.21, 0.67).

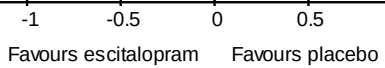
Clinical Global Impression – Improvement (CGI-I)

Results from the meta-analysis are presented in Figure B.6.4 to Figure B.6.6.

Figure B.6.4: CGI Improvement (LOCF) – 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 05 CGI Improvement (FAS LOCF) - a change characteristic - secondary endpoint
Outcome: 01 CGI Improvement (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
99012	177	2.55(1.05)	175	2.93(1.07)		53.99	-0.38 [-0.60, -0.16]
99270	162	2.38(1.16)	165	2.71(1.05)		46.01	-0.33 [-0.57, -0.09]
Subtotal (95% CI)	339		340			100.00	-0.36 [-0.52, -0.19]
Test for heterogeneity: Chi² = 0 09, df = 1 (P = 0.76), I² = 0%							
Test for overall effect: Z = 4.30 (P < 0.0001)							
Total (95% CI)	339		340			100.00	-0.36 [-0.52, -0.19]
Test for heterogeneity: Chi² = 0 09, df = 1 (P = 0.76), I² = 0%							
Test for overall effect: Z = 4.30 (P < 0.0001)							



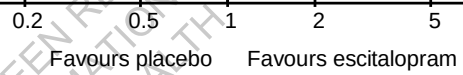
Source: Meta-analysis Report - Attachment 1

Figure B.6.5: Number and Percentage of Patients with CGI-I ≤2 (LOCF), also called 'responders' - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 06 Number of Patients with CGI-I <=2 (FAS LOCF) - secondary endpoint
Outcome: 03 Number of Patients with CGI-I <=2 (FAS LOCF) - 12 weeks

Study or sub-category	Escitalopram n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
99012	96/177	68/176		47.37	1.40 [1.12, 1.77]
99270	101/163	68/165		52.63	1.50 [1.21, 1.87]
Total (95% CI)	340	341		100.00	1.46 [1.24, 1.71]

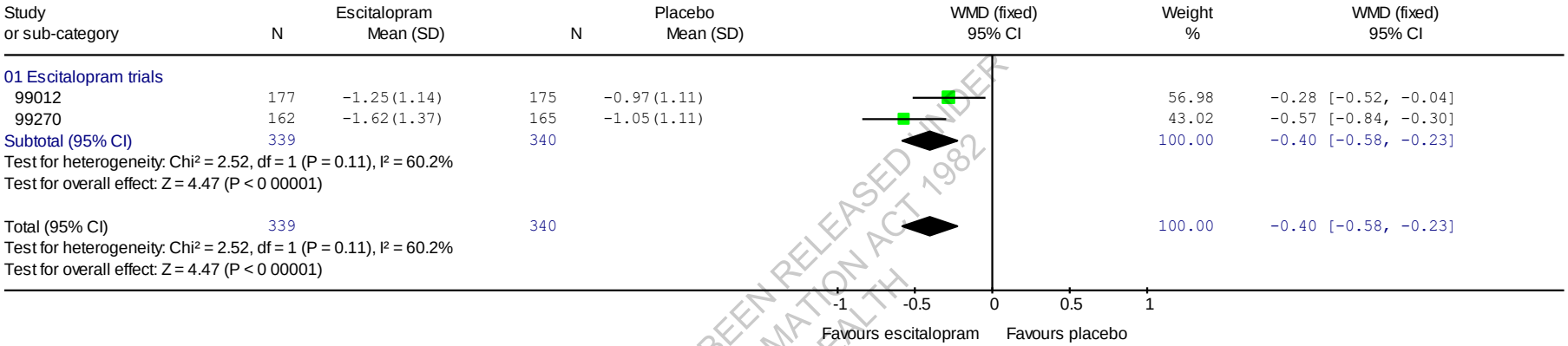
Total events: 197 (Escitalopram), 136 (Placebo)
Test for heterogeneity: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%
Test for overall effect: Z = 4.64 (P < 0.00001)



Source: Meta-analysis Report - Attachment 5

Figure B.6.6: Change in CGI Severity (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 04 Change in CGI Severity (FAS LOCF) - secondary endpoint
Outcome: 01 Change in CGI Severity (FAS LOCF) - "Head-to-Head" comparison - 12 weeks



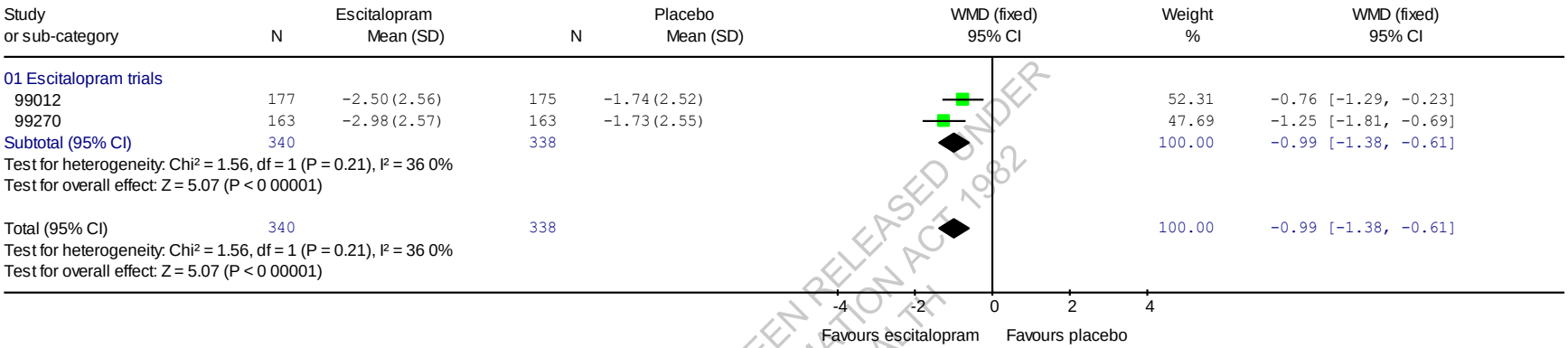
Source: Meta-analysis Report - Attachment 5

Sheehan Disability Scale (SDS)

Results from the meta-analysis are presented in Figure B.6.7 to Figure B.6.9.

Figure B.6.7: Change in SDS Work Scores (LOCF) - 12 weeks

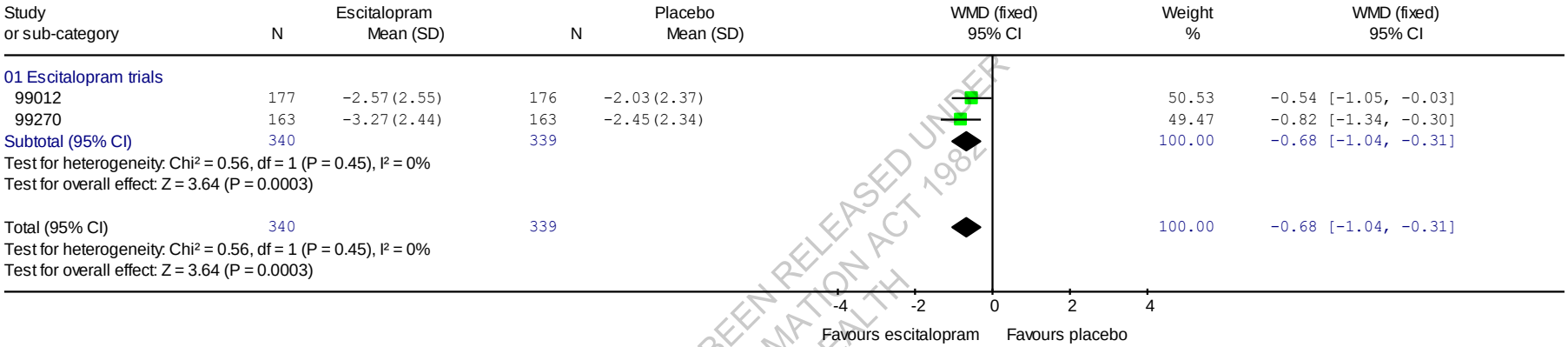
Review: Escitalopram (Lexapro) - SAD
Comparison: 07 Change in SDS Work Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Work Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks



Source: Meta-analysis Report - Attachment 5

Figure B.6.8: Change in SDS Social Scores (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 08 Change in SDS Social Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Social Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

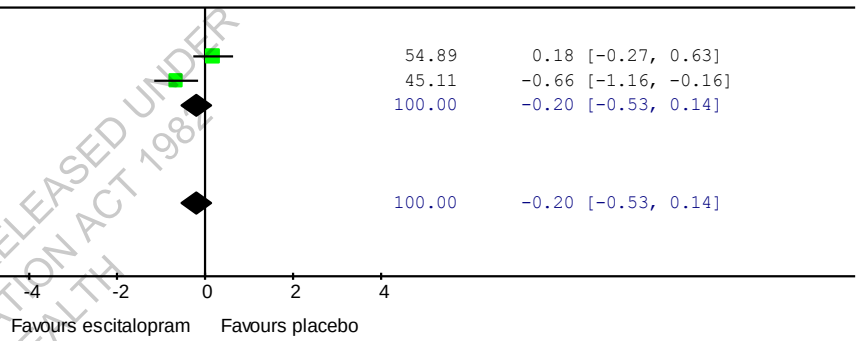


Source: Meta-analysis Report - Attachment 5

Figure B.6.9: Change in SDS Family Scores (LOCF) - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 09 Change in SDS Family Scores (FAS LOCF) - secondary endpoint
Outcome: 01 Change in SDS Family Scores (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
99012	177	-1.44(2.05)	176	-1.62(2.27)		54.89	0.18 [-0.27, 0.63]
99270	163	-2.00(2.41)	163	-1.34(2.17)		45.11	-0.66 [-1.16, -0.16]
Subtotal (95% CI)	340		339			100.00	-0.20 [-0.53, 0.14]
Test for heterogeneity: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%							
Test for overall effect: Z = 1.17 (P = 0.24)							
Total (95% CI)	340		339			100.00	-0.20 [-0.53, 0.14]
Test for heterogeneity: Chi² = 6.00, df = 1 (P = 0.01), I² = 83.3%							
Test for overall effect: Z = 1.17 (P = 0.24)							



Source: Meta-analysis Report - Attachment 5

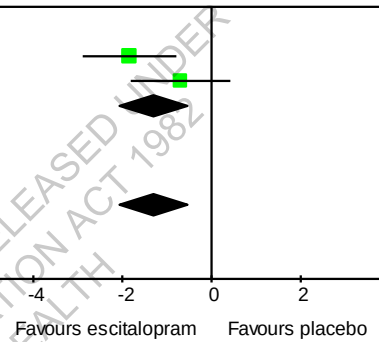
Montgomery and Åsberg Depression Rating Scale (MADRS)

Results from the meta-analysis are presented in Figure B.6.10.

Figure B.6.10: Change in MADRS Total Score (LOCF) - secondary endpoint - 12 weeks

Review: Escitalopram (Lexapro) - SAD
Comparison: 10 Change in MADRS Total Score (FAS LOCF) - secondary endpoint
Outcome: 01 Change in MADRS Total Score (FAS LOCF) - "Head-to-Head" comparison - 12 weeks

Study or sub-category	Escitalopram N	Escitalopram Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Escitalopram trials							
99012	175	-2.44(5.05)	170	-0.60(4.89)		53.06	-1.84 [-2.89, -0.79]
99270	159	-2.76(5.09)	158	-2.06(5.04)		46.94	-0.70 [-1.82, 0.42]
Subtotal (95% CI)	334		328			100.00	-1.30 [-2.07, -0.54]
Test for heterogeneity: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%							
Test for overall effect: Z = 3 35 (P = 0 0008)							
Total (95% CI)	334		328			100.00	-1.30 [-2.07, -0.54]
Test for heterogeneity: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%							
Test for overall effect: Z = 3 35 (P = 0 0008)							



Source: Meta-analysis Report - Attachment 5

s22 [redacted]

B.6.6 Summary of efficacy and safety

Change in mean LSAS total score was the primary outcome for Study 99270 and 99012, and a secondary outcome in Study 99269. s47E(d) [redacted] The LSAS is widely used in treatment studies, is sensitive, validated and considered the gold standard measure of treatment success in SAD. An improvement of 10 points on the LSAS (i.e. a mean Total Score difference of –10) is considered a clinically relevant treatment improvement[13]. Responders (based on LSAS criteria) have been defined as having a greater than or equal to 35-50% reduction in LSAS Total Score[13]. Similarly, a CGI-I score of $\leq$ 2 has also been used to define a responder to therapy, while a CGI-S score <2 suggests remission[13]. ***On all of these important response measures, escitalopram was shown to significantly improve patient outcomes, compared with the comparator.***

The improvement in LSAS scores seen in all three studies was statistically significant. The benefit of escitalopram was evident after 12 weeks of therapy and continued to increase from 12 to 24 weeks of therapy. In Study 99270, treatment with escitalopram 20mg daily resulted in a difference in mean LSAS total score change of -15.09 (95% CI -20.92, -9.25) at Week 24, while at 24 weeks in Study 99269 there was a difference of –12.82 (95% CI –16.95, -8.70), both compared with placebo. In all

three studies at both 12 and 24 weeks, a difference in mean improvement of –10 in LSAS Total Score fell within the 95% CIs for this outcome, providing a high level of confidence that a clinically meaningful result was obtained.

Responders to therapy, defined as either a 50% or greater reduction in LSAS total score or CGI-I ≤2, were also significantly greater with escitalopram. In Study 99270 at endpoint, 17.2% (95% CI 7.0%, 27.5%) of patients receiving escitalopram 10mg daily and 27.3% (95% CI 17.1%, 37.6%) more patients responded to escitalopram (based on LSAS criteria), compared with the comparator. Improvements in CGI-I responders also occurred. The percentage of CGI-S remitters (i.e. patients with a score of ≤2 on the CGI-S) were significantly greater with escitalopram. Eighteen percent (risk difference 17.8%, 95% CI 8.3%, 27.3%; escitalopram 10mg daily) and 27% (risk difference 26.6%, 95% CI 16.9%, 36.4%; escitalopram 20mg daily) more patients achieved remission at study endpoint, versus the comparator, based on CGI-S improvements.

Thus, escitalopram consistently improved patient outcomes on all key, patient-relevant efficacy outcome measures. This included mean improvement in the LSAS scale Total Score (≥10 point improvement) and percentage of responders (based on LSAS criteria), as well as responders based on CGI-I criteria. In addition, significantly more patients achieved remission (based on CGI-S criteria) with escitalopram. The results of the randomised, controlled, double-blind 24 week treatment studies presented demonstrate that therapy with escitalopram provides statistically significantly superior treatment (compared with placebo), across a range of outcomes, that is also clinically meaningful and relevant.

s22

B.8 Interpretation of the clinical evidence

Summary

Social Anxiety Disorder is a severe, disabling condition with significant negative patient impact on social functioning leading to educational, social and financial disadvantage. Information on the importance of pharmacotherapy in improving the lives of patients with SAD is presented.

The patients in the trials had been sufferers of SAD for 20-24 years and the mean age of onset was 15-18 years. This sample of patients closely mirrors the epidemiological evidence (see Attachment 2). At 12 weeks a greater proportion of these patients responded to treatment (when compared to placebo) and at 24 weeks an even larger response was seen. This was reinforced by the relapse prevention study. As would be expected, and shown in other studies, duration of treatment was important, with greater improvements seen over time.

Escitalopram provides superior efficacy and similar safety to the main comparator (placebo). A modelled economic evaluation is presented in Section C. This assessment is based on three well designed and conducted direct comparative randomised, controlled studies. The key study outcome (improvement in the LSAS Total Score) was significantly improved in the escitalopram treatment groups, compared with placebo in all studies.

The percentage of patients responding to therapy (based on LSAS and CGI-I criteria) and achieving remission (based on CGI-S criteria) were also significantly greater with escitalopram, demonstrating the overall superiority of escitalopram therapy across a range of patient-relevant outcomes. s22

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B.8.2 Assessment of the trial evidence for escitalopram in SAD

B.8.2.1 The level of the evidence

A comprehensive literature review was undertaken, with full details provided in Section B.1 and B.2. The three studies identified in the literature search and presented in the submission are all double-blind, randomised, controlled, multicentre, parallel-group **direct** comparisons between escitalopram and comparator (placebo). This is generally considered the highest level of clinical evidence available.

B.8.2.2 The quality of the evidence

The studies were well designed, conducted and reported, with full details provided in the Clinical Study Reports provided. Full details of the methods of randomisation, and blinding are provided in this submission. Randomisation was by a third party service (the pharmaceutical company). Blinding was maintained throughout the studies, with identical study products provided for each treatment group.

The basis of the analysis was 'intent to treat', based on all randomised patients with one valid post-baseline assessment of the primary outcome (a continuous variable). In all cases the results are presented using Last Observation Carried Forward methodology. The flow of participants through each of the studies is clearly identified in Section B.3.

Thus, the level of evidence provided in the submission is high, with the three studies presented all well conducted, randomised, controlled, double-blind, parallel group studies that provide a direct comparison with the comparator.

B.8.2.3 The statistical precision of the evidence

Efficacy and safety result data presented in Subsection B.6 for the individual direct randomised trial results and the pooled analyses was able to provide a high level of statistical precision. The primary efficacy results were presented as the difference between escitalopram and placebo in mean change from baseline to study endpoint in LSAS Total Score (with 95%CI). Secondary efficacy endpoints were presented as difference in mean change from baseline to endpoint with 95% CIs (continuous data), with dichotomous data also being reported as a relative risk (with 95% CI) and NNT (with 95% CI). Safety results were presented with relative risk (with 95%CI) and risk difference (with 95%CI).

B.8.2.4 The size of the effect

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all studies, treatment with escitalopram resulted in statistically and clinically significant improvements in LSAS Total Score, compared with placebo at

study endpoint. The clinical patient relevance of the improvements is discussed in Section B.8.5 below.

In the fixed-dose treatment Study 99270 at Week 24 the difference of the adjusted mean change was –7.45 (95% CI –13.29, -1.62) in the escitalopram 10mg group and –15.09 (95% CI –20.92, -9.25) in the escitalopram group, both compared with placebo.

In the flexible-dose treatment Study 99012 at Week 12 (study endpoint) the difference was –7.29 (95% CI –12.37, -2.21). In this study the mean dose of escitalopram was 17.1mg daily.

When meta-analysed the non-adjusted mean change between escitalopram versus placebo was -8.74 (95% CI -12.60, -4.89) at 12 weeks. This also needs to be considered in light of the final data point at 24 week mean change being -14.52. These results are depicted in summary table Table B.6.1.

The 24 weeks results, as expected, show a higher difference in the adjusted mean change in LSAS Total Score in the flexible-dose relapse prevention study –12.82 (95% CI –16.95, -8.70) for escitalopram (mean daily dose 17.3mg). The primary outcome in the relapse prevention study was time to relapse. The mean time to relapse was significantly greater, with a mean survival time of 135 days with escitalopram, compared with 103.5 days for placebo (Cox Hazard Ratio 2.83, P = 2.7E-08). **More than twice as many patients receiving placebo relapsed (91 with placebo versus 42 with escitalopram.**

Secondary Study Outcomes

The results of the key secondary outcomes (proportion of patients with ≥50% improvement in LSAS (LSAS responders), Clinical Global Impression – Improvement and Severity (CGI-I, CGI-S), % patients with CGI-I≤2 (CGI responders) and % patients with CGI-S≤2 (CGI-S remitters)) all improved with escitalopram therapy, with most improvements also being of statistical significance. The proportion of LSAS responders (patients with ≥50% change in LSAS Total Score) in Study 99270 was 17% greater with escitalopram 10mg daily (17.2%; 95%

risk difference CI 7.0, 27.5) and 27% greater with escitalopram 20mg daily (risk difference 27.3%; 95% CI 17.1%, 37.6%), compared with placebo at Week 24.

The CGI ≤2 (CGI responders) from the meta-analysis at 12 weeks confirms that patients are 46% more likely to respond on escitalopram than placebo at 12 weeks. This was slightly lower at 24 weeks at 39% but the difference was not statistically different. This can be seen in the summary Table B.8.1.

What is also clear is the consistency in the results reported across various outcome measures in terms of NNT, responders and remitters. Overall indicating that the body of evidence suggests that escitalopram is clinically significant.

Table B.8.1: Summary of secondary outcomes

(95% CI)			**Study 99270**		**Study 99012**
		week	**Escitalopram 10mg**	**Escitalopram 20mg**	**Escit. $\bar{x}$ =17.1mg**
NNT vs placebo					
	≥50% LSAS	*12*	**11** (6, 167)	**5** (4, 11)	
		24	**6** (4, 14)	**4** (3, 6)	
	CGI-I<2	*12*	**7** (4, 33)	**5** (3, 10)	**6** (4, 19)
		24	**13** (5, 32)	**5** (3, 11)	
	CGI-S<2	*12*	**9** (5, 37)	**7** (5, 20)	
		24	**6** (4, 12)	**4** (3, 6)	
Relative Risk vs placebo					
	≥50% LSAS	*12*	**1.42** (0.97, 2.08)	**1.91** (1.34, 2.72)	
		24	**1.61** (1.20, 2.15)	**1.96** (1.49, 2.59)	
	CGI-I<2	*12*	**1.33** (1.06, 1.67)	**1.50** (1.21, 1.87)	**1.40** (1.12, 1.77)
		Meta analysis 12		**1.46 (1.24, 1.71)**	
		24	**1.15** (0.94, 1.41)	**1.39** (1.16, 1.67)	
	CGI-S<2	*12*	**1.83** (1.14, 2.94)	**2.03** (1.27, 3.22)	
		24	**1.92** (1.33, 2.77)	**2.37** (1.67, 3.38)	
Difference in % of patients achieving vs placebo					
	≥50% LSAS	*12*	**8.7** (-0.6, 18.0)	**18.7** (8.9, 28.4)	
		24	**17.2** (7.0, 27.5)	**27.3** (17.1, 37.6)	
	CGI-I<2	*12*	**13.7** (3.0, 24.4)	**20.8** (10.2, 31.3)	**15.6** (5.3, 25.9)
		24	**7.6** (-3.1, 18.4)	**19.6** (9.3, 30.0)	
	CGI-S<2	*12*	**11.1** (2.7. 19.4)	**13.7** (5.1, 22.2)	
		24	**17.8** (8.3, 27.3)	**26.6** (16.9, 36.4)	

More patients receiving escitalopram had treatment-emergent adverse events, with the risk statistically significantly greater in two out of three of the studies. Total patients withdrawals in the two treatment groups were similar, as were withdrawals due to adverse events, with no statistically significant differences between the treatment groups in all studies. Patient withdrawals due to lack of efficacy were significantly reduced with escitalopram compared with placebo in the studies at week 24 (Study 99270: escitalopram 10mg RR 0.53, 95% CI 0.30 to 0.96, escitalopram 20mg RR 0.38, 95% CI 0.20 to 0.75; Study 99269: RR 0.43, 95% CI 0.30 to 0.62). In Study 99012 at Week 12 there was a non-significance trend in favour of escitalopram (RR 0.36, 95% CI 0.12, 1.10).

B.8.2.5 The clinical importance and patient-relevance of the effectiveness and safety outcomes

Liebowitz Social Anxiety Scale (LSAS)

Change in mean LSAS Total Score is the primary outcome in Study 99270 and 99012. While a variety of measurement scales have been developed to quantify the severity of SAD, the most widely used scale is the LSAS. It has been able to establish efficacy in a large number of placebo-controlled studies in SAD and is currently viewed as the gold standard[13]. s38 An improvement of at least 10 points on the LSAS has been suggested as showing a clinically relevant improvement, while patients demonstrating a ≥35-50% reduction in LSAS have been defined as treatment responders[13]. Study 99270 reported patients achieving a ≥50% reduction, rather than the potentially more relevant and easier to obtain ≥35%, i.e. the 'hurdle' to achieve response was perhaps higher in this study than necessary.

Interpreting the data for these disorders and determining the clinical significance of the results achieved can be complex.

The patients in the trials had been sufferers of SAD for 20-24 years and the mean age of onset was 15-18 years. This sample of patients closely mirrors the epidemiological evidence (see Attachment 2). Patients entering into the trials had a mean LSAS at baseline ranging between 95.44 to 96.32, thereby, classifying patients as having ***severe SAD***, (i.e. significant impairment). At the end of 12 weeks patients on escitalopram achieved a mean LSAS score ranging from 55.35-62.25 and at 24 weeks 32.28-39.80 (all results were statistically significantly better than placebo). Clinically, this translates into a patient improving from severe to moderate (and associated with less distress) or mild forms of SAD. Given that normal volunteers scored LSAS<30 the results achieved by patients on escitalopram suggests a clinically significant improvement.

The mean improvement, in LSAS scores in all three studies is statistically significant. The benefit of escitalopram was evident after 12 weeks of therapy and continued to increase from 12 to 24 weeks of therapy. In Study 99270, treatment with escitalopram 20mg daily resulted in a difference in an adjusted mean LSAS total score change of -15.09 (95% CI -20.92, -9.25) at 24 weeks, while at 24 weeks in Study 99269 there was a benefit of –12.82 (95% CI –16.95, -8.70), both compared with placebo.

These results were also seen in the unadjusted mean change from baseline, on which the meta-analysis was conducted. When meta-analysed the mean change between escitalopram versus placebo was -8.74 (95% CI -12.60, -4.89) at 12 weeks. This also needs to be considered in light of the 24 week mean change being -14.52 for study 99270. In all three studies and the meta-analysis at both 12 and 24 weeks, a difference in mean improvement of –10 on the LSAS fell within the 95% CIs for this outcome, providing a high level of confidence that a clinically meaningful result was obtained. In Study 99279, 17 to 27% more patients responded to therapy, based on the LSAS responders definition (risk difference 17.2%, 95% CI 7.0%, 27.5% with escitalopram 10mg daily; risk difference 27.3%, 95% CI 17.1%, 37.6% with escitalopram 20mg daily), both compared with placebo at Week 24.

The further improvement in the response to treatment on the LSAS scale between 12 and 24 weeks seen in these studies suggest that the 12 weeks short-term efficacy

results underestimate the fuller response to treatment observed with prolonged treatment to six months. Other available clinical trial evidence indicates that further mean improvement in the symptoms of SAD as measured on the LSAS total score beyond six months is likely[13]. Thus it would be expected that improvement much greater than a 10 point change on the LSAS scale would be seen if treatment duration was extended, given that statistically and clinically significant improvements of 11 points (Study 99269) and 15 points (escitalopram 20mg daily, Study 99270) were seen in the 24 week studies.

Clinical Global Impression– Improvement (CGI-I) and Severity (CGI-S)

CGI-I score results are secondary study outcomes in all the studies. The CGI-I scale has been used to identify responders to therapy, specifically patients reporting a score of 1 or 2 (*very much* or *much improved*) on the CGI-I scale have been defined as responding to therapy. Patients reporting a CGI-S score of ≤2 have been defined as remitters (i.e achieving disease remission). While these global scales are not recommended as primary scales, they may be useful as a secondary scale to help judge the clinical relevance of the finding[13].

The percentage of patients with CGI-I≤2 was greater with escitalopram than placebo in the two treatment studies in which it was measured. In the meta-analysis of Study 99270 and 99012 there was a 46% improvement with escitalopram compared with placebo (RR 1.46, 95% CI 1.24, 1.71). Significant improvement in response beyond 12 weeks did not occur. In Study 99270 remission based on the CGI-S scale was also assessed, with significantly more patients achieving remission at Weeks 12 and 24 with both 10mg and 20mg escitalopram daily. The improvement was 83-92% greater from Weeks 12-24 with escitalopram 10mg compared with placebo (Week 12: RR 1.83, 95% CI 1.14, 2.94; Week 24: RR 1.92, 95% CI 1.33, 2.77). A 103-137% greater improvement was seen with escitalopram 20mg daily (Week 12: RR 2.03, 95% CI 1.27, 3.22; Week 24: 2.37, 95% CI 1.67, 3.38; both versus placebo)

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The impact of co-morbidities on the effectiveness of treatment

The clinical trials excluded patients with co-morbidities, as recommended in clinical trials guidelines for SAD[13]. However approximately 50%-82.3% of patients with social phobia have comorbid mental, drug or alcohol problems.[28 29] Up to 23.6% of patients who present with social phobia have alcohol abuse problems; conversely, many patients presenting for treatment of substance abuse problems meet the criteria for social phobia.[30] Studies have shown that alcohol-related disorders occur twice as often in those affected by SAD than in those without.[18 31] Social phobia usually precedes alcohol abuse and about 20% of those treated for alcohol-related disorders have SAD.[32] If undetected, the risk of rapid relapse is high, since psychosocial treatments that are often a central aspect of treating alcohol abuse may be difficult or impossible to attend. Importantly, when SAD is treated in alcohol abusers, both social anxiety and alcohol use appear to improve.

Longitudinal data show that:

- Social phobia precedes approximately 70 percent of these comorbid conditions, suggesting that some comorbid conditions arise in response to the phobia[18 33]
- Social phobia may be a risk factor for other mental health issues[16 34] and is also associated with a more severe course and character of subsequent depressive illness[35]
- The presence of comorbidity in social phobia has been associated with an increased lifetime incidence of suicidal ideation and suicide attempts.[18]
- Comorbid disorders, particularly major depression, tend to be more prevalent in patients with an earlier onset of SAD and are associated with exacerbated disability and lower quality of life[36].

In an Australian study 21% of the people who met criteria for any mental disorder met criteria for three or more current disorders, and they accounted for 33% of the disability days and for 37% of the service use.[37] Comorbidity has serious consequences and, because of the linear nature of the relationships, is unlikely to be an artefact of the method of inquiry.

The co-occurrence of SAD and MDD is associated with greater impairment than SAD alone.[38] In a study that compared patients with SAD alone, patients with SAD and depression (MDD, dysthymia, or depressive disorder not otherwise specified (NOS)), and patients with SAD and comorbid anxiety disorders, those with SAD and depression had poorer overall functioning.[39] Furthermore, patients in the SAD and depression group reported an earlier age of onset of their SAD than did patients in the other two groups and had more severe social anxiety symptoms than patients in the SAD alone group.

Attachment 8 presents the clinical trial evidence (1 trial) regarding escitalopram treating people with SAD and comorbidities (with depression being the largest co-morbidity). Many of the symptoms of SAD overlap with those of depression and other anxiety disorders[40]. Individuals who present with anxiety, depression, alcohol- or substance-related disorders should be considered at high risk of undetected SAD. The

fear and avoidance in SAD is therefore, linked to feared social situations. Likewise, major depression frequently co-exists with SAD, presenting clinicians with the diagnostic challenge of distinguishing social withdrawal due to depression from fearful social avoidance.[41]

Table B.8.2 and Table B.8.3 present details regarding Olie et al (07).

Table B.8.2: Clinical Trial: Anxiety with comorbid depression

	Study Characteristics	Patient Characteristics	Outcomes Measured	Aims of Study
Olie JP et al 2007[42]	Multicentre, open label, non-randomised, prospective, naturalistic setting 12 weeks	Age: 18-82 yrs Females: 64% Dose: 10-20mg MDD: DSM-IV-TR N=790	Primary: MADRS Secondary HAM-A CGI-I CGI-S AEs	To assess any association between changes in the scores of depression rating scales over the study period and the scores of anxiety rating scales at baseline. To evaluate the safety and tolerability of Escitalopram in this patient population. To assess correlations between physician and patient measures of efficacy.

Table B.8.3: Details of Trial[42]

	% Co-morbidities	Population with Anxiety	HAM-A≥20
Olie JP et al (2007)[42]	SAD: 11% GAD: 27% Panic disorder: 10% OCD: 6% Agoraphobia: 4% PTSD: 3%	No anxiety:390/790 1 anxiety:349/790 ≥2 anxieties: 129 Incomplete information: 4/790	N=423

Outcomes from the trial are presented in and Table B.8.4:

Table B.8.4: Outcomes from Trial[42]

	MADRS (Primary)	HAMA	Responders ≥50% reduction HAMA % (CI)	Remitters HAMA<7	Responders CGI-I≤2
Change in patients with no anxiety	20.5	13.8			
Change in patients with ≥1 anxiety	18.3[i]	15.5[ii]			
All patients		10.8	69% (65.6-72.2%)	38.1% (34.7-41.6%)	70.8% (67.5-74%)

i: p<.0024 (LOCF) for patients with and without anxiety

ii: p<.0078 (LOCF) for patients with and without anxiety

Conclusions:[42]

a) The use of anxiolytics had no impact on the outcome
b) Of the 61% of patients experiencing a co-morbidity, results showed that anxiety symptoms as measured with the HAM-A, improved in parallel to the improvement in depressive symptoms, with escitalopram treatment.
c) Patients with at least one anxiety disorder had a greater improvement in HAM-A score than those without comorbid anxiety, but there was no statistically significant difference in the improvement in HAM-A scores as a function of baseline severity of depression, indicating that comorbid depression did not affect response to treatment of anxiety.

Evidence regarding the impact of treatment in co-morbidities is sparse and certainly does not meet Level 1 evidence. When pharmacotherapy is considered, upon examination of the 1 trial utilising escitalopram, it would seem that patients with at least one anxiety disorder and comorbid depression has a greater improvement in Hamilton Anxiety Scale (HAMA) score than those without comorbid anxiety (Table B.8.4). This would seem to indicate that at worst comorbid patients would respond similarly to those with pure depression and at best would show an improved outcome, when measured in terms of HAMA. As SAD in the main randomised, controlled trials was measured with LSAS it is hard to draw a conclusion on this measure.

B.8.2.6 The consistency of results over the three trials presented

The results in the three studies presented were generally consistent. All efficacy outcomes improved with escitalopram therapy, with most results achieving statistical significance. This was particularly evident with the primary outcome, difference in mean change in LSAS Total Score. There was generally a greater improvement with escitalopram 20mg daily compared with 10mg daily (Study 99270). Results achieved at 24 weeks were generally greater than those achieved after 12 weeks of therapy (Study 99270 and 99012).

Study 99012 was a relapse prevention study and thus the study design differed from the other two treatment studies. Prior to randomisation into this study, patients had received open-label escitalopram for 12 weeks, with responders then randomised to receive either escitalopram or placebo. Despite this difference in study design, the results occurring in this study were generally consistent with the other two studies (in which all patients were randomised to therapy, not specifically responders).

B.8.2.7 Classification of the therapeutic profile of escitalopram

Escitalopram has been demonstrated to be therapeutically superior to the comparator placebo, in Section B.6 and B.8, due to greater comparative effectiveness. The comparative safety is considered similar/non-inferior. While treatment-emergent adverse events are greater with escitalopram than placebo (as would be expected of an active treatment), total patient withdrawals and withdrawals due to adverse events are similar in the treatment studies. Withdrawals due to lack of efficacy were statistically significantly greater with placebo in the two longer term studies, in the 12 week meta-analysis and there was a strong trend towards significance in the 12 week study.

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PRODUCT INFORMATION

LEXAPRO® FILM-COATED TABLETS
LEXAPRO® ORAL SOLUTION

NAME OF THE MEDICINE

Escitalopram oxalate

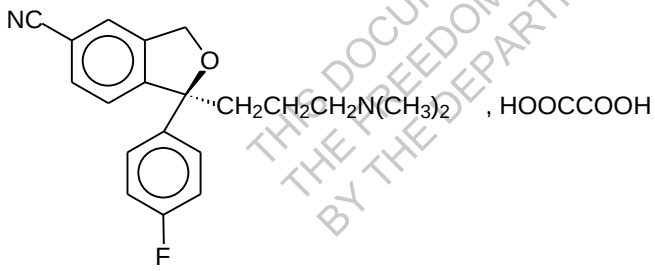
Chemical name:
S(+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrogen oxalate.

CAS number:
219861-08-2

Molecular formula:
$C_{20}H_{21}FN_2O$, $C_2H_2O_4$

Molecular weight:
414.42

Structural formula:



DESCRIPTION

Escitalopram is the active enantiomer (S-enantiomer) of citalopram. Escitalopram oxalate is a fine white to yellow, crystalline material.

Escitalopram oxalate is sparingly soluble in water, slightly soluble in acetone, soluble in ethanol and freely soluble in methanol. No polymorphic forms have been detected.

Lexapro 10 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "L" on one side.

Lexapro 20 mg tablets are oval, white, scored, film-coated tablets marked with "E" and "N" on one side.

Lexapro tablets contain the following excipients: cellulose - microcrystalline, silica - colloidal anhydrous, talc - purified, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

Lexapro oral solution is a clear, nearly colourless to yellowish solution. It contains the following excipients: sodium hydroxide and purified water.

PHARMACOLOGY

Pharmacological actions

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake (*in vitro* IC_{50} 2nM).

The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.

Escitalopram is a highly selective Serotonin Reuptake Inhibitor (SSRI). On the basis of *in vitro* studies, escitalopram had no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRIs, escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and DA D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity.

Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter.

Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing properties of the S-enantiomer in citalopram.

In healthy volunteers and in patients escitalopram did not cause clinically significant changes in vital signs, ECGs, or laboratory parameters.

S-demethylcitalopram, the main plasma metabolite, attains about 30% of parent compound levels after oral dosing and is about 5-fold less potent at inhibiting 5-HT reuptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing).

While the absolute bioavailability of escitalopram has not been studied, it is unlikely to differ significantly from that of racemic citalopram (about 80%).

Distribution
The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%.

Metabolism
Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28 - 31% and < 5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination
The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min.

Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Approximately 8.0% of escitalopram is eliminated unchanged in urine and 9.6% as the S-demethylcitalopram metabolite based on 20 mg escitalopram data. Hepatic clearance is mainly by the P450 enzyme system.

The pharmacokinetics of escitalopram are linear over the clinical dosage range. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Reduced hepatic function
In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Reduced renal function
While there is no specific data, the use of escitalopram in reduced renal function may be extrapolated from that of racemic citalopram. Escitalopram is expected to be eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Elderly patients (> 65 years)
Escitalopram pharmacokinetics in subjects > 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients.

Gender
In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Polymorphism
It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6 (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Lexapro should not be used for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and obsessive-compulsive disorder in children and adolescents under the age of 18 years since the safety and efficacy in this population have not been established.

Major Depression

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

Two fixed-dose studies and one flexible-dose study have shown escitalopram in the dose range 10 - 20 mg/day to be more efficacious than placebo in the treatment of depression.

All three studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Two of the studies included an active reference (citalopram). All three studies consisted of a 1-week single-blind placebo lead-in period followed by an 8-week double-blind treatment period.

Patients were required to have depression with a minimum score of 22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at both the screening and baseline visits. The MADRS consists of 10 items that measure core symptoms of depression, such as sadness, tension, pessimism and suicidal thoughts. Each item is rated on a scale of 0 (no abnormality) to 6 (severe). The populations studied were therefore defined as suffering from moderate to severe depression (mean MADRS score 29). A total of 591 patients received escitalopram in these studies.

All three studies showed escitalopram to be statistically significantly superior to placebo on the ITT LOCF analysis of the mean change from baseline in the MADRS total score ($p \leq 0.01$). The magnitude of the difference between escitalopram and placebo in the MADRS change score ranged from 2.7 to 4.6 (mean of these values: 3.6). The magnitude of the difference for citalopram ranged from 1.5 to 2.5 (mean of these values: 2.0). The magnitude of the difference is larger with escitalopram than with citalopram.

Escitalopram demonstrated a significant early difference compared to placebo from week 2 onwards on the MADRS (week 1 in observed cases analysis). Likewise, the Clinical Global Impression–Improvement items (CGI-I) differed significantly from placebo from week 1 onwards. These early differences were not seen with racemic citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend towards greater improvement in patients with severe major depressive disorder (HAM-D > 25) receiving 20 mg/day as compared to 10 mg/day. The Hamilton Rating Scale for Depression (HAM-D) consists of 17 to 24 items reflecting core symptoms of depression. Each item is scored on a 3, 4, or 5 point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

In a fourth flexible-dose study with a similar design, the primary analysis did not distinguish a significant drug/placebo difference for either escitalopram or citalopram over 8 weeks on the MADRS change score in the LOCF dataset. However, on the basis of the OC analysis, both escitalopram and citalopram were significantly better than placebo ($p \leq 0.05$; difference between escitalopram and placebo: 2.9).

Escitalopram demonstrated efficacy in the treatment of anxiety symptoms associated with depression. In the three positive double-blind placebo-controlled studies escitalopram was shown to be effective compared to placebo on the MADRS anxiety items; inner tension and sleep disturbances. Furthermore, in the one study where the Hamilton Anxiety Scale (HAM-A) and the anxiety factor of the Hamilton Depression Rating Scale (HAM-D scale) were used, results have shown that escitalopram was significantly better than placebo.

In a relapse prevention trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week open-label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation of escitalopram at the same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined as a decrease of the MADRS total score to ≤ 12.

Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo (26% vs. 40%; hazard ratio=0.56, p=0.013).

Further evidence of long-term efficacy is provided in a 6-month study which compared escitalopram 10 mg/day to citalopram 20 mg/day over a 6-month treatment period. Analysis of the primary endpoint (the development of the MADRS total scores over 24 weeks) demonstrated escitalopram to be at least as efficacious as citalopram in the long-term treatment of depression. Secondary analyses showed that, while both treatments resulted in numerical improvements in ratings in the MADRS, HAM-A and the CGI, escitalopram was statistically superior to citalopram in several analyses, both during and at the end of the study.

Additional supportive evidence of the sustained efficacy of escitalopram treatment is demonstrated in an open-label 12-month study. The efficacy of escitalopram was maintained throughout the study, as measured by the MADRS total score and CGI-S score. Patients showed continued improvement, with total MADRS scores falling from 14.2 at baseline to 5.8 at last assessment, and CGI-scores falling from 2.7 at baseline to 1.6 at last assessment.

A study in the elderly did not provide conclusive efficacy results for escitalopram, as the reference drug (fluoxetine) failed to differentiate from placebo. However, safety data from this study showed escitalopram to be well tolerated.

Generalised Anxiety Disorder (GAD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of Generalised Anxiety Disorder was demonstrated in three 8-week placebo-controlled flexible-dose studies (10 to 20 mg per day) and one 12-week fixed-dose, active-reference (paroxetine 20 mg/day), study (5, 10 and 20 mg per day).

In the four studies, the mean HAM-A total scores at baseline ranged from 22.1 to 27.7 and the CGI-S scores were 4.2 or higher, indicating significant GAD symptomatology.

In all three placebo-controlled, flexible-dose studies, escitalopram was significantly better than placebo at endpoint on the primary efficacy measure (mean change from baseline to endpoint in HAM-A total score), and the results were supported by secondary efficacy measures.

In the fixed-dose study, over a 12-week period, escitalopram in doses of 10 and 20 mg/day was statistically significantly more effective than placebo on the primary measure of efficacy, with an effect size at least as high as that of the reference treatment paroxetine. The 5 mg dose of escitalopram was numerically, but not statistically significantly, superior to placebo. 10 mg escitalopram was statistically significantly superior to the reference treatment paroxetine (LOCF) based on the HAM-A and CGI-I.

Table 1

Study	**Mean Treatment Difference in Change from Baseline in HAM-A Total Scores (LOCF) [95% CI]**	
	8 weeks	**12 weeks**
Flexible-dose		
ESC to PBO	-1.6* [-3.2 ; -0.0]	-
Flexible-dose		
ESC to PBO	-1.48* [-2.83; -0.13]	-
Flexible-dose		
ESC to PBO	-3.49*** [-4.93; -2.04]	-
Fixed-dose		
ESC5 to PBO	-	-1.29 [-3.13; 0.54]
ESC10 to PBO	-	-2.56** [-4.40; -0.73]
ESC20 to PBO	-	-2.15* [-3.99; -0.31]
PAR20 to PBO	-	-0.51 [-2.33; 1.32]
ESC20 to PAR20	-	-1.65# [-3.49; 0.20]

*p≤0.05; **p≤0.01; ***p≤0.001; #p≤0.05 *versus* PAR

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

In the pooled analysis of these three placebo-controlled, flexible-dose studies of similar design, the mean change from baseline in HAM-A total score improved statistically significantly (LOCF) over time in the escitalopram group relative to the placebo group. The separation from placebo was first observed at week 1 and continued through to the end of the study (week 8). The treatment difference to placebo at week 8 was –2.3 in favour of escitalopram ($p \leq 0.01$).

The results of the primary analysis (pooled data) were supported by secondary LOCF analyses (pooled data), where escitalopram was statistically significantly superior to placebo on the HAM-A psychic anxiety subscale score ($p \leq 0.001$), the HAM-A item 1 (anxious mood) score ($p \leq 0.001$), and the HAM-A item 2 (tension) score ($p \leq 0.01$). Escitalopram was also more effective than placebo on the CGI-S score ($p \leq 0.01$) and on the CGI-I score at week 8 ($p \leq 0.001$). The results on the HAD anxiety subscale, the HAM-A somatic subscale, the HAM-D anxiety scale, the Covi Anxiety Scale (OC), and the QoL (OC) also showed superior efficacy of escitalopram relative to placebo at week 8 ($p \leq 0.05$).

The long-term efficacy of escitalopram in the treatment of GAD is based on the results from the double-blind active comparator study, an open-label extension study and a double-blind, randomised, placebo-controlled relapse prevention study.

The active comparator study demonstrated numerically superior efficacy of escitalopram over paroxetine both on the primary efficacy measure (mean change from baseline in HAM-A total score) and on the secondary efficacy measures (mean change from baseline in HAM-A psychic anxiety, CGI-S, QoL, HAM-A somatic anxiety, HAM-A item 1 (anxious mood), HAM-A item 2 (tension), HAM-D anxiety and Covi scores, and mean CGI-I score) at week 24. For all but one (QoL) of the efficacy measures, a further improvement was seen from week 8 to week 24. In the primary efficacy analysis, the extra improvement in mean HAM-A total score over the last 16 weeks of treatment was 2.3 points for escitalopram compared with 1.6 points for paroxetine.

Further evidence of long-term efficacy is provided by an open-label extension study, which showed a beneficial effect of continued treatment with escitalopram. In this study, escitalopram treatment was associated with additional improvement beyond the response observed during the initial 8 weeks of treatment in the lead-in studies. The mean change in HAM-A total score from baseline (final visit of the lead-in study) to week 24 (LOCF) was -3.8, with greater improvement observed in patients who were switched from placebo in the lead-in study to escitalopram in the extension study (4.9 points versus 2.7 points for those previously treated with escitalopram). Similar positive results were seen in the analyses of secondary efficacy measures.

Escitalopram 20 mg/day significantly reduced the risk of relapse in a 24- to 76-week randomised continuation study in 373 patients who had responded during the initial 12-week open-label treatment.

Social Anxiety Disorder (SAD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

The efficacy of escitalopram in the treatment of SAD was demonstrated in three placebo-controlled clinical studies. A short-term, flexible-dose (10 to 20 mg/day) study, a long-term,

fixed-dose (5, 10, and 20 mg/day), active-reference (paroxetine 20 mg/day) study, and a relapse prevention study.

Approximately two-thirds of patients in the studies were markedly or severely ill (score of 5 or 6 on the CGI-S) and one-third were moderately ill (score of 4 or less on the CGI-S). The mean baseline LSAS total score ranged from 92 to 96 in the three studies.

In the short-term, flexible-dose study, over a 12-week period, escitalopram was statistically significantly better than placebo on the primary, and almost all the secondary measures of efficacy (see Table 2).

In the placebo-controlled, active-reference study, escitalopram was effective both in the short- and in the long-term (see Table 2), with an effect size at least as high as that of the reference treatment paroxetine (escitalopram 20 mg/day was significantly superior to the reference treatment paroxetine 20 mg/day from week 16 and onwards (OC)). Thus, continued treatment with escitalopram improves treatment response. At week 24 of the study, all three doses of escitalopram also produced significant improvements in the LSAS subscale scores for fear/anxiety and avoidance, the CGI-I score (except for the 10 mg dose of escitalopram), the CGI-S score, and the SDS subscale scores for work, social life, and family life.

Table 2

Study	**Mean Treatment Difference in Change from Baseline in LSAS Total Scores (LOCF) [95% CI]**	
	12 weeks	**24 weeks**
Short-term, flexible-dose		
ESC to PBO	-7.29** [-12.37; -2.21]	-
Long-term, fixed-dose		
ESC5 to PBO	-9.18*** [-14.40; -3.95]	-10.46*** [-16.27; -4.66]
ESC10 to PBO	-5.07† [-10.32; 0.18]	-7.45** [-13.29; -1.62]
ESC20 to PBO	-10.31*** [-15.56; -5.06]	-15.09*** [-20.92; -9.25]
PAR20 to PBO	-9.83*** [-15.04; -4.61]	-11.82*** [-17.62; -6.03]
ESC20 to PAR20	-	-3.26 [-9.07; 2.54]

*p≤0.05; **p≤0.01; ***p≤0.001; †p=0.059

ESC = escitalopram; ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PAR20 = paroxetine 20 mg; PBO = placebo

The beneficial effect of long-term treatment with escitalopram was also reflected in the analyses of responders and remitters in this study. The analyses showed a further increase both in the proportion of responders and in the proportion of remitters from week 12 to week 24, especially in the escitalopram 20 mg group. At week 24, a statistically significantly greater proportion of responders and remitters were seen in all three escitalopram dose groups (except for the proportion of responders in the 10 mg group) than in the placebo group (p≤0.01) (see Tables 3 and 4).

Table 3

Long-term, fixed-dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	41	50
ESC5	61***	67**
ESC10	55*	58
ESC20	62***	70***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 4

Long-term, fixed-dose study	**Remitters (CGI-S ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	13	19
ESC5	29***	39***
ESC10	24*	37***
ESC20	27**	46***

*p≤0.05; **p≤0.01; ***p≤0.001

ESC5 = escitalopram 5 mg; ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

In the relapse prevention study, the primary efficacy analysis showed a statistically significantly superior effect of escitalopram relative to placebo on the time to relapse of SAD (log-rank test, p≤0.001). Furthermore, patients treated with escitalopram had fewer protocol-defined relapses than those treated with placebo. In addition, patients treated with escitalopram showed a further improvement in mean LSAS total score during the double-blind period, while patients treated with placebo showed deterioration. Escitalopram was also statistically significantly superior to placebo at week 24 on all the secondary efficacy measures in this study: the LSAS total score, the LSAS subscale scores for fear/anxiety and avoidance, the CGI-S score, and the SDS subscale scores for work, social life, and family life (p≤0.001).

Obsessive-Compulsive Disorder (OCD)

Lexapro should not be used in the treatment of children and adolescents under the age of 18 years.

Efficacy of escitalopram in the treatment of OCD was investigated in two clinical trials, a 24-week placebo-controlled, fixed-dose study (with efficacy assessments at week 12 and week 24) and a 16 + 24-week placebo-controlled relapse prevention study.

Patients included in these studies were male and female outpatients aged 18 – 65 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria and a pre-defined minimum score of 20 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Patients had actual baseline Y-BOCS scores of approx. 27, indicating significant OCD symptomatology. A structured clinical interview, the

Mini International Neuropsychiatric Interview (MINI), was used to assist in the diagnosis and to exclude relevant psychiatric comorbidities. In order to avoid the confounding variable of significant concomitant depression, patients with more than mild depressive symptoms, i.e. a score of 22 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS), were excluded. To ensure a relatively homogenous population with OCD, patients currently diagnosed with any other psychiatric disorders as per Axis I of DSM-IV-TR or any clinically significant unstable medical illness were also excluded.

Results at week 12 of the 24-week placebo-controlled, fixed-dose study are shown in Tables 5 and 6. In the short-term (**12 weeks**), 20 mg/day escitalopram separated from placebo on the Y-BOCS total score.

Table 5

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 12 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-1.97 [-3.97; 0.02]
ESC20 to PBO	-3.21* [-5.19; -1.23]

*p≤0.01

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Furthermore, escitalopram 20 mg/day was significantly more efficacious than placebo on the Y-BOCS subscale of rituals at week 12. Both escitalopram 10 mg/day and escitalopram 20 mg/day were significantly more efficacious than placebo on the Y-BOCS subscale of obsessions as well as on the NIMH-OCS total score, CGI-I score and CGI-S score.

Table 6

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 12 (FAS, LOCF, ANCOVA) [95% CI]**				
	Y-BOCS Obsessional Subscore	**Y-BOCS Compulsive Subscore**	**NIMH-OCS Score**	**CGI-I Score**	**CGI-S Score**
ESC10 to PBO	-1.15* [-2.20; -0.10]	-1.01 [-2.04; 0.01]	-1.01** [-1.70; -0.33]	-0.36* [-0.66; -0.06]	-0.41* [-0.72; -0.09]
ESC20 to PBO	-2.05*** [-3.10; -1.01]	-1.34** [-2.37; -0.32]	-1.40*** [-2.08; -0.72]	-0.53*** [-0.83; -0.23]	-0.64*** [-0.95; -0.33]

*p≤0.05; **p≤0.01; ***p≤0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Results after **24 weeks** showed that both escitalopram 10 mg/day (p<0.05) and escitalopram 20 mg/day (p<0.01) were significantly more efficacious than placebo as measured by the primary outcome measure, the Y-BOCS total score, as well as on the secondary subscales of Y-BOCS (obsessions and rituals) and the NIMH-OCS score (escitalopram 10 mg/day (p<0.01) and escitalopram 20 mg/day (p<0.001)).

Table 7

Long-term (24 weeks) fixed-dose study	**Mean Change from Baseline to Week 24 in Y-BOCS Total Score (FAS, LOCF, ANCOVA) [95% CI]**
ESC10 to PBO	-2.56* [-4.93; -0.20]
ESC20 to PBO	-3.55** [-5.90; -1.20]

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

The beneficial efficacy of long-term treatment with escitalopram was also demonstrated by the analyses of responders and remitters in this study as shown in Tables 8 and 9.

Table 8

Long-term (24 weeks) fixed-dose study	**Responders (CGI-I ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	38.9	38.1
ESC10	50	58*
ESC20	57.9*	56.1*

ESC (10 or 20 mg) vs PBO: *p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Table 9

Long-term (24 weeks) fixed-dose study	**Remitters (CGI-S ≤ 2) (LOCF) (%)**	
	12 weeks	**24 weeks**
PBO	11.5	26.5
ESC10	24.1*	41.1*
ESC20	28.1**	38.6

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.01
ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; PBO = placebo

Maintenance of efficacy and prevention of relapse were investigated in the relapse prevention study. This 24-week relapse prevention study was preceded by a 16-week open-label period with patients initially receiving escitalopram 10 mg/day. In case of lack of efficacy (as judged by the investigator), the dose could be increased to a maximum of 20 mg/day. If dose-limiting adverse effects occurred, it was permissible to decrease the dose to 10 mg/day. Thus the dose of escitalopram was flexible at 10 - 20 mg/day from week 2 to 12. Subsequently, the dose was fixed at the dose received at the end of week 12 until week 16 to allow stabilisation of the patient on this dose. Responders to treatment were defined as patients with a decrease in Y-BOCS total score from baseline by ≥ 25% at week 16, and remitters were defined as Y-BOCS ≤ 10. See Table 10 for responder and remitter rates at the end of the 16-week open-label phase.

Table 10

Relapse prevention study (16-week open-label, flexible-dose phase)	**Responders (Reduction of Y-BOCS ≥ 25%) (APTS I, LOCF) (%)**	**Remitters (Y-BOCS ≤ 10) (APTS I, LOCF) (%)**
ESC	74.4	34.0

ESC = escitalopram 10 & 20 mg

Responders at the end of the above 16-week open-label treatment phase (escitalopram 10 mg: 30 responders; escitalopram 20 mg: 133 responders) entered the 24-week randomised, double-blind placebo-controlled relapse prevention phase. Both escitalopram 10 mg/day (p=0.014) and 20 mg/day (p<0.001) showed significantly fewer relapses as seen in Table 11.

Table 11

Relapse prevention study (24-week double-blind phase)		**n**	**Number of relapses**	**% relapsed**
10 mg dose group	ESC10	30	3	10.00*
	PBO	20	7	35.00
20 mg dose group	ESC20	133	35	26.32**
	PBO	137	74	54.01
10 - 20 mg dose group	ESC	163	38	23.31**
	PBO	157	81	51.59

ESC (10 or 20 mg) vs PBO: *p≤0.05; **p≤0.001

ESC10 = escitalopram 10 mg; ESC20 = escitalopram 20 mg; ESC = escitalopram 10 & 20 mg; PBO = placebo

INDICATIONS

Treatment of major depression.
Treatment of social anxiety disorder (social phobia).
Treatment of generalised anxiety disorder.
Treatment of obsessive-compulsive disorder.

CONTRAINDICATIONS

Hypersensitivity to citalopram, escitalopram and any excipients in Lexapro (see DESCRIPTION).

Monoamine Oxidase Inhibitors - Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see Interactions with other medicines). Some cases presented with features resembling serotonin syndrome (see ADVERSE EFFECTS).

Escitalopram should not be used in combination with a MAOI. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 14 days should elapse after discontinuing escitalopram treatment before starting a MAOI or RIMA.

Pimozide - Concomitant use in patients taking pimozide is contraindicated (see Interactions with other medicines).

PRECAUTIONS

Clinical worsening and suicide risk - The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

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

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses of 24 short-term (4 to 16-week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive-compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants

compared to placebo in adults beyond the age of 24 years, and there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Akathisia/psychomotor restlessness - The use of SSRIs/SNRIs 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.

Haemorrhage **-** Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymoses, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Lexapro should therefore be used with caution in patients concomitantly treated with oral anticoagulants, medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

Hyponatraemia **-** Probably due to inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia has been reported as a rare adverse reaction with the use of SSRIs. Especially elderly patients seem to be a risk group.

Seizures **-** The drug should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency (see ***Preclinical safety***).

Diabetes **-** In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Mania - SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (electroconvulsive therapy) - There is limited published clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advised.

Effects on ability to drive and use machines - Escitalopram does not impair intellectual function and psychomotor performance. However, as with other psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Discontinuation - Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt.

The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. 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 escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see DOSAGE AND ADMINISTRATION).

Cardiac disease - Escitalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, escitalopram causes a small decrease in heart rate. Consequently, caution should be observed when escitalopram is initiated in patients with pre-existing slow heart rate.

Impaired hepatic function - In subjects with hepatic impairment, clearance of escitalopram was decreased and plasma concentrations were increased. The dose of escitalopram in hepatically impaired patients should therefore be reduced (see Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Impaired renal function - Escitalopram is extensively metabolised and excretion of unchanged drug in urine is a minor route of elimination. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) and escitalopram should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

Preclinical safety - High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 8-fold greater than anticipated clinically, have been associated with convulsions, ECG abnormalities and cardiovascular changes in experimental animals. Of the cardiovascular changes, cardiotoxicity (including congestive

heart failure) was observed in comparative toxicological studies in rats following oral escitalopram or citalopram administration for 4 to 13 weeks and appears to correlate with peak plasma concentrations although its exact mechanism is not clear. Clinical experiences with citalopram, and the clinical trial experience with escitalopram, do not indicate that these findings have a clinical correlate.

Effects on fertility

No fertility studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Use in pregnancy

Category C.

No relevant epidemiological data or well controlled studies in pregnant women are available for escitalopram. SSRIs have had limited use in pregnancy without a reported increase in birth defects.

Neonates should be observed if maternal use of Lexapro continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Neonates exposed to Lexapro, other SSRIs (Selective Serotonin Reuptake Inhibitors), or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (< 24 hours) after delivery.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced foetal weight at systemic exposure levels (based on AUC) ca. 11-fold that anticipated clinically, with no effects seen at 6-fold. No teratogenicity was evident in this study at relative systemic exposure levels of ca. 15 (based on AUC).

There were no peri/postnatal effects of escitalopram following oral dosing of pregnant rats (conception through to weaning) at systemic exposure levels (based on AUC) ca. 2-fold that anticipated clinically. However, the number of stillbirths was increased and the size, weight and postnatal survival of offspring were decreased at a relative systemic exposure level ca. 5.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed and only after careful consideration of the risk/benefit.

Use in lactation
It is expected that escitalopram, like citalopram, will be excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4 - 5.1% (below the notional 10% level of concern).

Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use of escitalopram in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

Paediatric use (children and adolescents < 18 years)
The efficacy and safety of escitalopram has not been established in children and adolescents less than 18 years of age. Consequently, escitalopram should not be used in children and adolescents less than 18 years of age.

Use in the elderly (> 65 years)
Escitalopram AUC and half-life were increased in subjects ≥ 65 years of age compared to younger subjects in a single-dose and a multiple-dose pharmacokinetic study. The dose of escitalopram in elderly patients should therefore be reduced (see DOSAGE AND ADMINISTRATION).

Carcinogenicity
No carcinogenicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

Citalopram did not show any carcinogenic activity in long-term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity
No genotoxicity studies were performed with escitalopram. However, other nonclinical studies suggest that the effects of escitalopram can be directly predicted from those of the citalopram racemate.

In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

Interactions with other medicines
MAOIs - Co-administration with MAO inhibitors may cause serotonin syndrome (see CONTRAINDICATIONS).

Pimozide - Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction with citalopram noted at a low dose of pimozide, concomitant administration of escitalopram and pimozide is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs - Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, *Hypericum perforatum* (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan - There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Medicines affecting the central nervous system - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold - SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

Hepatic enzymes - Escitalopram has a low potential for clinically significant drug interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A4, and a weak inhibitor of 2D6.

Effects of other drugs on escitalopram in vivo

The pharmacokinetics of escitalopram was not changed by co-administration with ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram.

Co-administration of escitalopram with omeprazole (a CYP2C19 inhibitor) resulted in a moderate (approximately 50%) increase in plasma concentrations of escitalopram and a small but statistically significant increase (31%) in the terminal half-life of escitalopram (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Co-administration of escitalopram with cimetidine (moderately potent general enzyme inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluoxetine, fluvoxamine, lansoprazole, and ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement (see also Poor metabolisers of CYP2C19 under DOSAGE AND ADMINISTRATION).

Effects of escitalopram on other drugs in vivo

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when escitalopram and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with metoprolol (a CYP2D6 substrate) resulted in a twofold increase in the plasma levels of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with escitalopram.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc) – Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Lexapro.

Alcohol - The combination of SSRIs and alcohol is not advisable.

ADVERSE EFFECTS

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually decrease in intensity and frequency with continued treatment and generally do not lead to a cessation of therapy. Data from short-term placebo-controlled studies are presented below. The safety data from the long-term studies showed a similar profile.

Treatment Emergent Adverse Events with an Incidence of ≥ 1% in placebo-controlled trials

Figures marked with * in the table below indicate adverse reactions where the incidence with escitalopram is statistically significantly different from placebo (p<0.05).

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
Patients Treated	1795	2632
Patients with Treatment Emergent Adverse Event	1135 (63.2)	1891 (71.8)
GASTROINTESTINAL SYSTEM DISORDERS		
nausea	151 (8.4)	481 (18.3)*
diarrhoea	91 (5.1)	207 (7.9)*
mouth dry	74 (4.1)	152 (5.8)*
constipation	42 (2.3)	71 (2.7)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
abdominal pain	47 (2.6)	68 (2.6)
vomiting	29 (1.6)	54 (2.1)
dyspepsia	30 (1.7)	33 (1.3)
flatulence	15 (0.8)	31 (1.2)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	305 (17.0)	506 (19.2)
dizziness	64 (3.6)	147 (5.6)*
paraesthesia	13 (0.7)	35 (1.3)
migraine	17 (0.9)	23 (0.8)
tremor	15 (0.8)	33 (1.3)
PSYCHIATRIC DISORDERS		
insomnia	82 (4.6)	245 (9.3)*
somnolence	62 (3.5)	217 (8.2)*
anorexia	12 (0.7)	56 (2.1)*
libido decreased	21 (1.2)	102 (3.9)*
anxiety	44 (2.5)	77 (2.9)
appetite decreased	8 (0.5)	35 (1.3)*
agitation	6 (0.3)	33 (1.3)*
nervousness	13 (0.7)	25 (1.0)
dreaming abnormal	18 (1.0)	41 (1.6)
impotence [gs]	4 (0.6)	22 (2.2)*
RESPIRATORY SYSTEM DISORDERS		
upper respiratory tract infection	91 (5.1)	96 (3.6)
coughing	18 (1.1)	24 (0.9)
rhinitis	81 (4.8)	146 (5.5)
sinusitis	24 (1.3)	46 (1.7)
pharyngitis	44 (2.5)	57 (2.2)
yawning	3 (0.2)	58 (2.2)*
bronchitis	31 (1.7)*	26 (0.9)
BODY AS A WHOLE - GENERAL DISORDERS		
influenza-like symptoms	65 (3.6)	87 (3.3)
fatigue	62 (3.5)	230 (8.7)*
back pain	61 (3.4)	74 (2.8)
SKIN AND APPENDAGES DISORDERS		
sweating increased	27 (1.5)	145 (5.5)*
MUSCULOSKELETAL SYSTEM DISORDERS		
arthralgia	22 (1.2)	27 (1.0)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

System Organ Class and Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
REPRODUCTIVE DISORDERS, FEMALE		
anorgasmia [gs]	3 (0.3)	47 (2.9)*
METABOLIC AND NUTRITIONAL DISORDERS		
weight increase	20 (1.1)	45 (1.7)
REPRODUCTIVE DISORDERS, MALE		
ejaculation disorder [gs]	3 (0.5)	48 (4.7)*
ejaculation failure [gs]	1 (0.2)	27 (2.7)*
CARDIOVASCULAR DISORDERS		
hypertension	24 (1.3)*	13 (0.5)
HEART RATE AND RHYTHM DISORDERS		
palpitation	15 (0.8)	30 (1.1)
SECONDARY TERMS		
inflicted injury (unintended injury)	22 (1.2)	23 (0.8)

* = Statistically significant difference escitalopram vs placebo (p<0.05) [gs] = gender specific

Adverse Events in Relation to Dose

The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg escitalopram groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg escitalopram treated patients (66%) was similar to that of the placebo treated patients (61%), while the incidence rate in 20 mg/day escitalopram treated patients was greater (86%). Common adverse events that occurred in the 20 mg/day escitalopram group with an incidence approximately twice that of the 10 mg/day escitalopram group and approximately twice that of the placebo group are shown below.

Incidence of common adverse events* in patients with major depression receiving placebo, 10 mg/day Lexapro, or 20 mg/day Lexapro

Adverse Event	Placebo (n=311)	10 mg/day Lexapro (n=310)	20 mg/day Lexapro (n=125)
Insomnia	4%	7%	14%
Diarrhoea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	< 1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*adverse events with an incidence rate of at least 5% in either escitalopram group and with an incidence rate in the 20 mg/day escitalopram group that was approximately twice that of the 10 mg/day escitalopram group and the placebo group.

Vital Sign Changes
Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment.

ECG Changes
Electrocardiograms from escitalopram, racemic citalopram, and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically relevant changes in pulse rate for any one treatment group. In all treatment groups (including placebo), there was a small increase in the mean adjusted QTcB interval: 1.8 msec for escitalopram and 2.0 msec for racemic citalopram, compared to 1.7 msec for placebo. Neither escitalopram nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Weight Changes
Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes
In clinical studies, there were no signals of clinically important changes in either various serum chemistry, haematology, and urinalysis parameters associated with escitalopram treatment compared to placebo or in the incidence of patients meeting the criteria for potentially clinically significant changes from baseline in these variables.

For abnormal laboratory changes registered as either *uncommon events* or *serious adverse events from ongoing trials* and observed during (but not necessarily caused by) treatment with Lexapro, please see Other Events Observed during the Premarketing Evaluation of Lexapro.

<u>Other Events Observed during the Premarketing Evaluation of Lexapro</u>

Following is a list of WHO terms that reflect adverse events occurring at an incidence of < 1% and serious adverse events from ongoing trials. All reported events are included except those already listed in the table or elsewhere in the Adverse Effects section, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it.

Events are further categorised by body system and are listed below. Uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients.

Application Site Disorders
Uncommon: otitis externa, cellulitis.

Body as a Whole
Uncommon: allergy, aggravated allergy, allergic reactions, asthenia, carpal tunnel syndrome, chest pain, chest tightness, fever, hernia, leg pain, limb pain, neck pain, oedema, oedema of extremities, peripheral oedema, rigors, malaise, syncope, scar.

Cardiovascular Disorders, General
Uncommon: hypertension aggravated, hypotension, hypertension, abnormal ECG.

Central and Peripheral Nervous System Disorders
Uncommon: ataxia, dysaesthesia, dysequilibrium, dysgeusia, dystonia, hyperkinesia, hyperreflexia, hypertonia, hypoaesthesia, leg cramps, lightheadedness, muscle contractions, nerve root lesion, neuralgia, neuropathy, paralysis, sedation, tetany, tics, twitching, vertigo.

Gastrointestinal System Disorders
Uncommon: abdominal cramp, abdominal discomfort, belching, bloating, change in bowel habit, colitis, colitis ulcerative, enteritis, epigastric discomfort, gastritis, gastroesophageal reflux, haemorrhoids, heartburn, increased stool frequency, irritable bowel syndrome, melaena, periodontal destruction, rectal haemorrhage, tooth disorder, toothache, ulcerative stomatitis.

Hearing and Vestibular Disorders
Uncommon: deafness, earache, ear disorder, otosalpingitis, tinnitus.

Heart Rate and Rhythm Disorders
Uncommon: bradycardia, tachycardia.

Liver and Biliary System Disorders
Uncommon: bilirubinaemia, hepatic enzymes increased.

Metabolic and Nutritional Disorders
Uncommon: abnormal glucose tolerance, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperlipaemia, thirst, weight decrease, xerophthalmia.

Musculoskeletal System Disorders
Uncommon: arthritis, arthropathy, arthrosis, bursitis, costochondritis, fascitis plantar, fibromyalgia, ischial neuralgia, jaw stiffness, muscle cramp, muscle spasms, muscle stiffness, muscle tightness, muscle weakness, myalgia, myopathy, osteoporosis, pain neck/shoulder, tendinitis, tenosynovitis.

Myo-, Endo- and Pericardial and Valve Disorders
Uncommon: myocardial infarction, myocardial ischaemia, myocarditis, angina pectoris.

Neoplasm
Uncommon: female breast neoplasm, ovarian cyst, uterine fibroid.

Platelet, Bleeding and Clotting Disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Poison Specific Terms
Uncommon: sting.

Psychiatric Disorders
Uncommon: aggressive reaction, amnesia, apathy, bruxism, carbohydrate craving, concentration impairment, confusion, depersonalisation, depression, depression

aggravated, emotional lability, excitability, feeling unreal, forgetfulness, hallucination, hypomania, increased appetite, irritability, jitteriness, lethargy, loss of libido, obsessive-compulsive disorder, panic reaction, paroniria, restlessness aggravated, sleep disorder, snoring, suicide attempt, thinking abnormal.

Red Blood Cell Disorders
Uncommon: anaemia hypochromic, anaemia.

Reproductive Disorders / Female
Uncommon: amenorrhoea, atrophic vaginitis, breast pain, genital infection, intermenstrual bleeding, menopausal symptoms, menorrhagia, menstrual cramps, menstrual disorder, premenstrual tension, postmenopausal bleeding, sexual function abnormality, unintended pregnancy, dysmenorrhoea, vaginal haemorrhage, vaginal candidiasis, vaginitis.

Reproductive Disorders / Male
Uncommon: ejaculation delayed, prostatic disorder.

Resistance Mechanism Disorders
Uncommon: moniliasis genital, abscess, infection, herpes simplex, herpes zoster, infection bacterial, infection parasitic, infection (tuberculosis), moniliasis.

Respiratory System Disorders
Uncommon: asthma, dyspnoea, laryngitis, nasal congestion, nasopharyngitis, pneumonia, respiratory tract infection, shortness of breath, sinus congestion, sinus headache, sleep apnoea, tracheitis, throat tightness.

Skin and Appendages Disorders
Uncommon: acne, alopecia, dermatitis, dermatitis fungal, dermatitis lichenoid, dry skin, eczema, erythematous rash, furunculosis, onychomycosis, pruritus, psoriasis aggravated, rash, rash pustular, skin disorder, urticaria, verruca.

Secondary Terms
Uncommon: accidental injury, bite, burn, fall, fractured neck of femur, alcohol problem, traumatic haematoma, cyst, food poisoning, lumbar disc lesion, surgical intervention.

Special Senses Other, Disorders
Uncommon: dry eyes, eye irritation, taste alteration, taste perversion, visual disturbance, ear infection NOS, vision blurred.

Urinary System Disorders
Uncommon: cystitis, dysuria, facial oedema, micturition frequency, micturition disorder, nocturia, polyuria, pyelonephritis, renal calculus, urinary frequency, urinary incontinence, urinary tract infection.

Vascular (Extracardiac) Disorders
Uncommon: cerebrovascular disorder, flushing, hot flush [gs], ocular haemorrhage, peripheral ischaemia, varicose vein, vein disorder, vein distended.

Vision Disorders
Uncommon: accommodation abnormal, blepharospasm, eye infection, eye pain, mydriasis, vision abnormal, vision blurred, visual disturbance.

White Cell and Reticuloendothelial System Disorders
Uncommon: leucopenia.

In addition the following adverse reactions have been reported with racemic citalopram (all of which have also been reported for other SSRIs):

Disorders of metabolism and nutrition – hyponatraemia, inappropriate ADH secretion (both especially in elderly women).

Neurological disorders – convulsions, convulsions grand mal and extrapyramidal disorder, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and inco-ordination).

Skin disorders - ecchymoses, angioedema.

Furthermore a number of adverse reactions have been listed for other SSRIs. Although these are not listed as adverse reactions for escitalopram or citalopram, it cannot be excluded that these adverse reactions may occur with escitalopram. These SSRI class reactions are listed below:

Cardiovascular disorders - postural hypotension.

Hepatobiliary disorders - abnormal liver function tests.

Neurological disorders - movement disorders.

Psychiatric disorders - mania, panic attacks.

Renal and urinary disorders - urinary retention.

Reproductive disorders - galactorrhoea.

Other Events Observed During the Postmarketing Evaluation of Escitalopram

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported in association with escitalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section:

Stomatitis, drug interaction NOS, feeling abnormal, hypersensitivity NOS, non-accidental overdose, injury NOS.

In addition, although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment subsequent to the marketing of racemic citalopram and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, anaphylaxis, choreoathetosis, delirium, dyskinesia, epidermal necrolysis, erythema multiforme, gastrointestinal haemorrhage, haemolytic anaemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinaemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

DOSAGE AND ADMINISTRATION

Adults
Escitalopram is administered as a single oral dose and may be taken with or without food. The oral solution can be mixed with water, orange juice or apple juice.

Major depression
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily.

Usually 2 - 4 weeks are necessary for antidepressant response, although the onset of therapeutic effect may be seen earlier. The treatment of a single episode of depression requires treatment over the acute and the medium term. After the symptoms resolve during acute treatment, a period of consolidation of the response is required. Therefore, treatment of a depressive episode should be continued for a minimum of 6 months.

Social anxiety disorder
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily. Social anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Generalised anxiety disorder
The recommended dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily. Generalised anxiety disorder is a disease with a chronic course and long-term treatment is therefore warranted to consolidate response and prevent relapse.

Obsessive-compulsive disorder
The recommended starting dose is 10 mg (one 10 mg tablet or 1 mL of the oral solution) once daily. Depending on individual patient response, the dose may be increased to 20 mg (one 20 mg tablet or 2 mL of the oral solution) daily.

Long-term treatment has been studied for a maximum of 40 weeks. Patients responding to a 16-week open-label treatment phase were randomised to a 24-week placebo-controlled relapse prevention phase, receiving 10 or 20 mg escitalopram daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (> 65 years of age)
A longer half-life and a decreased clearance have been demonstrated in the elderly. 10 mg (one 10 mg tablet or 1 mL of the oral solution) is the recommended maximum maintenance dose in the elderly (see Pharmacokinetics and PRECAUTIONS).

Children and adolescents (< 18 years of age)
Safety and efficacy have not been established in this population. Escitalopram should not be used in children and adolescents under 18 years of age (see PRECAUTIONS).

Reduced hepatic function
An initial dose of 5 mg (half a 10 mg tablet or 0.5 mL of the oral solution) daily for the first two weeks of treatment is recommended. Depending on individual patient response, the

dose may be increased to 10 mg (one 10 mg tablet or 1 mL of the oral solution) (see PRECAUTIONS).

Reduced renal function
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min) (see PRECAUTIONS).

Poor metabolisers of CYP2C19
For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg (half a 10 mg tablet or 0.5 mL of the oral solution) daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg (one 10 mg tablet or 1 mL of the oral solution) (see Pharmacokinetics and Interactions with other medicines under PRECAUTIONS).

Discontinuation
Significant numbers of discontinuation symptoms may occur with abrupt discontinuation of escitalopram. To minimise discontinuation reactions, tapered discontinuation over a period of at least one to two weeks is recommended. If unacceptable discontinuation symptoms occur following a decrease in the dose or upon discontinuation of treatment then resuming the previously prescribed dose may be considered. Subsequently, the dose may be decreased but at a more gradual rate.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

Toxicity
Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Doses between 400 and 800 mg of escitalopram alone have been taken without any severe symptoms. No fatalities or sequelae were reported in the few cases with a higher dose (one patient survived ingestion of either 2,400 or 4,800 mg).

Symptoms
Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), the cardiovascular system (hypotension, tachycardia, arrhythmia and ECG changes (including QT prolongation)), and electrolyte/fluid balance conditions.

Treatment
There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Lexapro tablets
- Film-coated tablets containing 10 mg or 20 mg escitalopram (as oxalate).
- Blister packs of 28 tablets.

Lexapro solution
- Oral solution containing 10 mg/mL escitalopram (as oxalate).
- 28 mL solution in brown glass bottle with a screw cap with childproof closure and syringe.

Storage conditions

Lexapro tablets:	Store below 30°C.
Lexapro solution:	Store below 25°C. Store the opened oral solution below 25°C. Discard after 3 months.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine

DATE OF APPROVAL

Date of TGA approval: 27 April 2007

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ATTACHMENT 2

EPIDEMIOLOGY OF GENERALISED ANXIETY DISORDER (GAD)

Table of Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	
GAD	Generalized Anxiety Disorder
EDSP	Early Developmental Stages of Psychopathology
ESEMed	European Study of the Epidemiology of Mental Disorders
GHS	German Health Interview and Examination Survey
HARP	The Harvard/Brown Anxiety Research Program
ICPE	International Consortium in Psychiatric Epidemiology
LASA	Longitudinal Aging Study Amsterdam
MDD	Major Depressive Disorder
NCS	National Comorbidity Study
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NSMHW	National Survey of mental Health and Well-being
US	United States

GAD Overview

Generalized anxiety disorder (GAD) is characterized by chronic and uncontrollable worrying and somatic anxiety, such as tension, hypervigilance and insomnia [1] The sufferer knows that the worry is excessive or unrealistic but feels unable to control it. The worry is associated with symptoms such as restlessness, fatigue, difficulty concentrating, irritability, muscle tension or sleep disturbance.[2] GAD is highly associated with other psychiatric disorders, and this comorbidity increases the economic and personal burden and severity of the disorder[1 3 4].

A re-analysis of the National Comorbidity Survey Replication that introduced a measure of severity, showed that GAD severity predicts the onset of secondary disorders, with more severe GAD associated with a higher risk of secondary disorders (comorbidities).[5]

Some of the symptoms associated with GAD are as follows (3 of these symptoms. Of at least moderate severity, should be present for a diagnosis)[6]:

- Restlessness or feeling 'on edge'
- Easily tired
- Concentration difficulties or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling or staying asleep or unsatisfying sleep)

These symptoms were also commonly reported in a Hong Kong study[7], where the three most commonly reported symptoms were:

- ''easily tired'',
- ''easily irritable'' and
- ''difficult to concentrate''.

Over half of the GAD subjects reported palpitations and bowel problems.[7] GAD subjects were more likely than sub-threshold GAD subjects to report ten of the eleven symptoms

examined, depressed mood for two or more weeks, suicidal ideation, cigarette smoking and alcohol use[7]. Other concerns were over finances, work performance and studies.

An American study[8] found that in a sample of primary care patients (N=1,029), approximately 1 in 10 met the criteria for GAD (DSM-IV) and these patients were more likely to suffer from somatic pain.

The following case study describes a GAD patient:

"The patient is a 54-year-old man who has been worrying excessively about activities of daily living in general and his health in particular for several years. He recently read about leukaemia and asked his primary physician to perform a bone marrow aspiration to rule out the disease. A hypochondriac, he fears that his minor physical ailments (such as headaches, coughing and sneezing) are masking a deadly disease. He is also convinced that his 33 year old son, who is mildly overweight, is going to die soon of heart disease, and he is doing his utmost to convince his son to lose the excess weight.

The patient is a successful businessman, husband and father of several children; an athlete; a pointer –even a decorated war veteran. Despite his achievements, however, the patient feels "miserable" and "tortured" by his persistent worries. He anticipates and dreads poor outcomes of even routine activities. He feels he cannot go to the movies because he might be unable to get a parking spot. He is convinces that people disregard him because he is short. He believes his wife is entirely unsympathetic to his plight. He now seeks medical advice."[9]

Clinical Features

GAD is categorised as an independent disorder.[10] The clinical diagnostic criteria for GAD are provided in Table 1.

Table 1 Diagnostic Criteria for Generalised Anxiety Disorder[11]

DSM IV Criteria for the Anxiety Disorders: Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not, for at least 6 months, about a number of events or activities (such as work or school performance).

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not, for the past 6 months). Note: Only one item is required in children.

- restlessness or feeling keyed up or on edge
- being easily fatigued
- difficulty concentrating or mind going blank
- irritability
- muscle tension
- sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, eg, the anxiety or worry is not about having a panic attack (as in Panic Disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during post-traumatic stress disorder.

E. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

F. The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a Pervasive Developmental Disorder.

Aetiology of GAD and worry

A generic model of GAD proposed by Barlow incorporates biological, psychological and environmental factors (an abridged version of the model is presented in Figure 1).[12] Barlow conceptualizes GAD as anxious apprehension and, suggests that it is the 'basic' anxiety disorder.

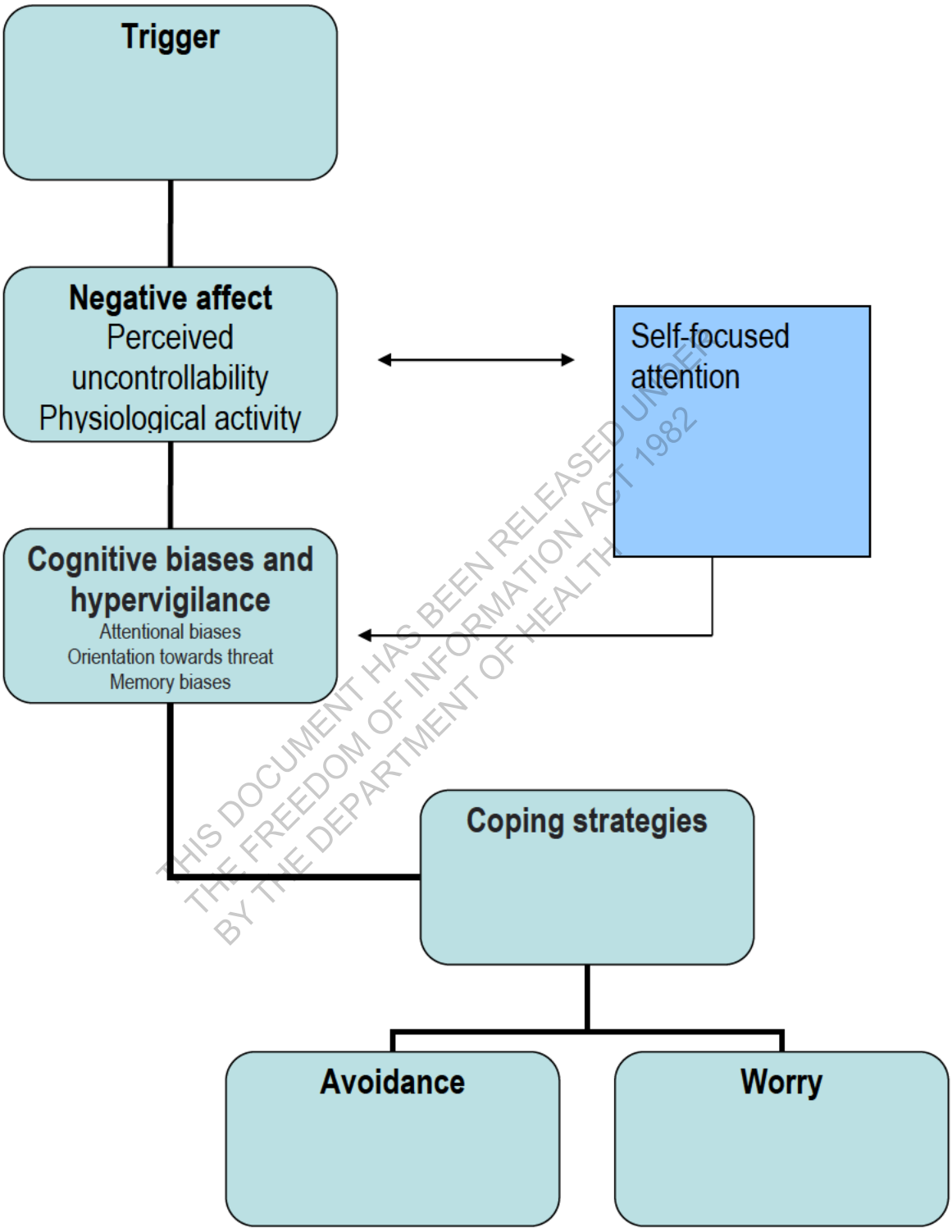
The model suggests that an individual has biological and psychological vulnerabilities which, if triggered will result in negative affect.[12] The negative affect is characterized by a sense of uncontrollability and is accompanied by supportive physiology and activation of specific brain circuits (e.g. the behavioural inhibition system). The individual becomes self-focused (e.g. on their physiological arousal) and hypervigilant for threat, which results in attempts to cope with the anxiety. Predominant coping strategies are behavioural avoidance or worry in an attempt to solve problems and reduce negative affect. It is important to note that behavioural avoidance is quite common in GAD: one study reported that 65% of patients avoided specific triggering stimuli, with social situations being most common.[13]

Results from the twin studies suggest a modest role for genetics with an estimated heritability of approximately 30–40% for both men and women (vs 70% heritability for major depression).[14] It should be noted that the largest proportion of the variance in liability for GAD is due to individual environmental factors.

Early environmental factors that are considered to be important in the development of GAD are:[6]

- Insecure attachment in childhood which is adulthood develop into beliegs that the world is a dangerous place, worry becomes an effective coping strategy.
- A traumatic childhood experience
- Parental separation
- Lack of opportunity for social interactions
- Modeling of a relative who has an anxiety disorder.

Figure 1Process of anxious apprehension[12]



Epidemiology

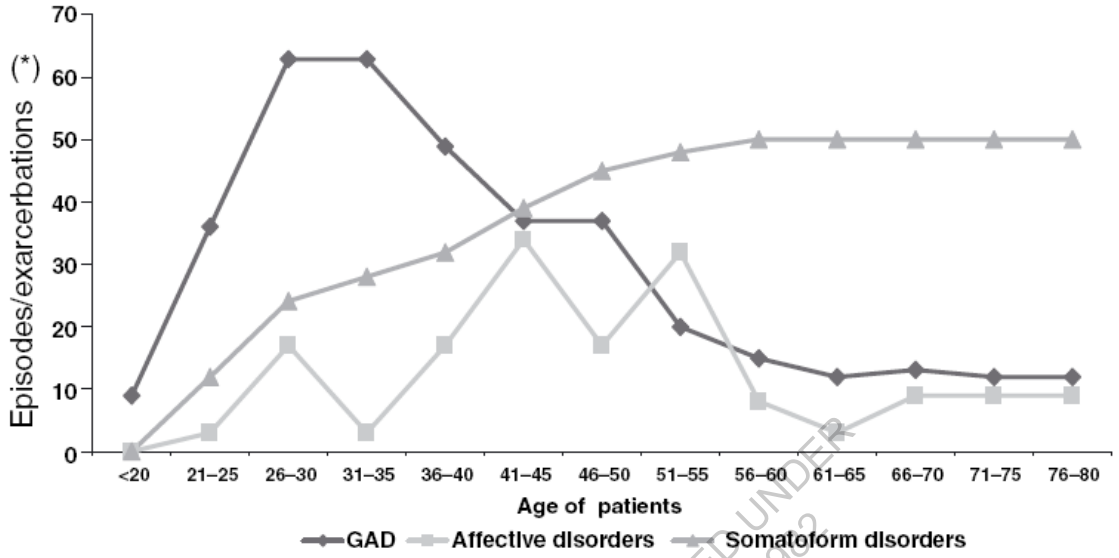
In general, anxiety disorders develop relatively early in life.[15] In 80–90% of cases, the disorder manifests before the age of 35, and the time between 10 and 25 years seems to be a high-risk period for the development of anxiety disorders. With GAD, the average first manifestation is between 25 and 30 years. GAD is the only anxiety disorder to show increased prevalence in the elderly.

In a 40 year longitudinal study of GAD patients (DSM-II-R) the course of the disorder was followed.[16] Between 1950-61, 512 people were admitted to the Lopez Neuropsychiatric Research Institute in Spain. A total of 370 of the original patients were contacted in 1984-2000 and of those 209 agreed to participate in the study. They were interviewed and 65 were diagnosed with GAD during the period of 1984-88. These patients were followed up during 1997-2000 (n=59).

The mean age of onset of GAD was 25.6 years and the mean episode length was 7.4 months; periods of remission or total remission of anxiety symptoms was uncommon.[16] There is however evidence to suggest that unlike other anxiety disorders, GAD is most common among older age groups.[17] See Figure 2 which shows that the majority of cases are in the 25-35 age group.

Social phobia (12%) and simple phobia (70%) were present before the appearance eof GAD, whilst the rest of the comorbid disorders usually emerged afterwards.[16] The course of development is presented in Figure 2.[16] It can be seen that, anxiety disorders peaked during the third and fourth decades of life and decreased thereafter. From age 30 the somatoform disorders emerged, together with major depression and alcohol dependence; finally, from age 50, dysthymia appeared. USD (undifferentiated somatoform disorder) was very frequent as a chronic clinical condition. The main symptoms recorded were somatic complaints about pain, and gastrointestinal and cardiopulmonary symptoms. These complaints had caused patients to see a doctor, and their worry about symptoms was not considered uncontrolled.

Figure 2 Course of patients with generalized anxiety disorder. [16]



(*) Percentage of patients with episodes or exacerbations of psychiatric disorders

Notes:

Affective disorders: major depression or dysthymia

Somatoform disorders: somatization disorder, hypochondria or undifferentiated somatoform disorder (USD)

The study found that :

(i) a low percentage of subjects were chronically affected by GAD after age 50;

(ii) with age, GAD tends to be replaced by somatizations (USD); and

(iii) worse prognosis was determined by lack of regular compliance, gender (female) and early onset of GAD.

In relation to the natural history of the disorder and the replacement, with age, of GAD by somatoform disorders, these results are in line with those of classic works. [18] The replacement of GAD by undifferentiated somatization disorder (USD) could be interpreted from two different points of view.[19] USD in these patients could reflect a change in the way they cope with anxiety. It has been suggested that in addition to the classic fight-or-flight reaction to chronic stress, the aged respond in a way that is more adaptative (freeze-reaction). The freeze response would not necessarily produce anxiety, but the elderly would be more likely to focus on their somatic state.[20] From an alternative

point of view, USD may constitute a minor form of GAD in older subjects . Older adults report more worries about health and fewer concerns about work compared with younger adults. Also, habituation to anxiety can decrease the number and severity of anxiety symptoms. Therefore, GAD in older patients could be characterized by vague and persistent complaints about health with mild levels of anxiety. These clinical symptoms could lead to a diagnosis of undifferentiated somatization disorder in older subjects [21 22].

Generally GAD has been associated with various medical conditions.[23 24] The susceptibility to comorbid conditions differs between male and female sufferers. Among males, particularly high rates were found for dermatologic (75%), arthritic (27%), and cardiac problems (20%), and among females, gastrointestinal problems (63%), allergies (52%), back pain (50%), migraine (42%), metabolic disorders (27%), and neurologic disorders (8%).[23 24] Similar results were observed in a French study though the rates were lower[25]. To secure successful remission, therefore, physician treatment choices must address not only the symptoms of GAD, but also current or probable comorbidities and any underlying causality.

Prevalence

Interpreting the epidemiological evidence[26]

Stage 1

Many of the earliest studies were based on DSM-III criteria (APA, 1980). DSM-III defined GAD as 1 month of persistent anxiety accompanied by associated symptoms from three of four categories.[5] DSM-III allowed GAD to be diagnosed only if patients did not meet the criteria for any other anxiety or affective disorder. It also separated generalised anxiety disorder from panic disorder. This was considered to create confusion because GAD was a residual category.[27]

Stage 2

DSM-III-R changed the requirements to 6 months of worry along with 6 of 18 associated symptoms to improve the validity of separation from normal anxiety and from anxiety that occurs secondary to other mental disorders (American Psychiatric Association, 1987).[5] An example of how this change has impacted on the estimation of the prevalence of GAD is shown by relaxing the requirement of excessive worry more days than not occurring for at least 6 months (requirement for DSM-III-R) to 1 month (requirement for DSM-III). A re-analysis of the National Comorbidity Survey Replication using this change showed that prevalence increased by about 50-60%.[5]

Stage 3

DSM-IV made further changes aimed at sharpening the characterization of GAD by requiring that worry be excessive and uncontrollable (American Psychiatric Association, 1994). DSM-IV also stipulated that the worry in GAD must be associated with at least three of six symptoms of tension and vigilance, and cause significant distress or impairment.[5] An example of how this change has impacted on the estimation of the prevalence of GAD is shown by relaxing the requirement of **excessiveness of worry** in DSM-IV, re-analysis of the National Comorbidity Survey Replication showed that prevalence increased by about 40%.[5] The authors also found that increasingly broader definitions of GAD are associated with decreasing rates of co-morbidity. One of the criticisms levelled at DSM-IV is that the 6-month duration and excessive-worry requirements, appear to miss individuals who suffer from significant generalized anxiety, and who also have an elevated risk of developing additional disorders. This has been found in other studies, with concerns that patients suffering from symptoms of GAD are being excluded inappropriately.[28] [29]

The changes seen in the classification of GAD and the epidemiologic evidence that eventuated suggest that GAD is a common disorder that, although often comorbid with other mental disorders, does not have a rate of comorbidity that is higher than those found in most other anxiety or mood disorders.[30]

The above description of the changes in DSM from III to IV, leave little doubt that GAD is now classified as a severe disorder that produces significant distress or impairment.

Table 2 summarises the key features of DSM-III, DSM-III-R and DSM-VI. The key differences in DSM changes from DSM-III-R to DSM-VI being[31]:

- "unrealistic/excessive anxiety and worry about two or more life circumstances" in the DSM-III-R to "excessive (but not unrealistic) anxiety and worry about more than one life circumstance" in the DSM-IV to which "difficulties to control the worry" was added.
- In the DSM-IV, the ancillary symptoms were further reduced and involve only 3 of 6 symptoms, selected from the categories of motor tension and vigilance, whereas the autonomic category was deleted.
- With associative features, "mild depressive symptoms are common," according to the DSM-III and DSM-III-R, whereas in the DSM-IV, in addition to depressive symptoms, the severity of which is unspecified, symptoms of muscle tension and somatic symptoms were added.
- Finally, impairment, which in the DSM-III and DSM-III-R was considered "only mild," is considered in the DSM-IV as "producing significant distress or impairment".

Therefore it is clear from this evidence that DSM-IV defined GAD patients are a severe group of GAD patients. Further DSM-IV defined patients are a more restrictive group of patients that would not include a large proportion of DSM-III-R patients. This is the key reason why the submission will look at DSM-IV patients alone, given that these were the basis of the Escitalopram trial.

Table 2 Shift in Criteria to Diagnose GAD[31]

Criteria	DSM-III	DSM-III-R	DSM-IV
Anxiety	Persistent anxiety	Unrealistic/excessive anxiety and worry (apprehensive expectation) about two or more life circumstances	**Excessive anxiety and worry (apprehensive expectation) about a number of events or activities; difficult to control (includes overanxious disorder of childhood)**
Duration	1 months	6 months	6 months
Ancillary symptoms	Unspecified number of symptoms from three of four categories	≥ 6 of 18 specified symptoms	**≥ 3 of 6 specified symptoms**
Symptoms and symptom categories	Apprehensive expectation	Motor tension (n = 4)	Restlessness/mental tension
	Motor tension	Autonomic (n = 9)	Fatigue
	Autonomic	Vigilance (n = 5)	Poor concentration
	Vigilance		Irritability
			Muscle tension
			Sleep disturbance
Associated features	Mild depression symptoms	Mild depressive symptoms	Muscle tension
			Somatic symptoms
			Depressive symptoms
			Exaggerated startle response
Impairment in social and occupational functioning	Rarely more than mild	Rarely more than mild	**Significant distress and impairment**
Exclusions	Not caused by another mental disorder such as depression or schizophrenia	Anxiety/worry, unrelated to another disorder (e.g., panic)	Anxiety/worry, unrelated to another disorder (e.g., panic)
		Does not occur during mood disorder or psychotic disorder	Does not occur during mood disorder or psychotic disorder
		Not organic (e.g., hyperthyroidism, caffeine intoxication)	Not organic (e.g., hyperthyroidism, caffeine intoxication)
		Not substance abuse related	Not substance abuse related

A summary of the prevalence data is presented in Table 3 Lifetime Prevalence of GAD. The lifetime prevalence ranged from 2.3-5.1% and 0.4-5.7% for DSM -III-R and DSM-IV respectively.

Australian Prevalence

In 1997 in Australia, 9.7% (1,299,900) people suffered an anxiety disorder, usually social phobia, generalised anxiety disorder or post-traumatic stress disorder.[32 33] The 12 month prevalence of GAD in Australia was 3.1% (females 3.7% and males 2.4%). This is within the range (thought the lower range) of that reported in the literature for other countries.

Table 3 Lifetime Prevalence of GAD

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
Iceland[34]	31.1%			
Cristchurch NZ[35]	21.7			
LASA[36] N=3,056 (55-85 years)	7%			
NCS (USA)[3] N=8,098 (15-54 years)		5.1%		
Nemesis (Netherlands)[37] N=7,076 (18-64 years)		2.3%		
Oslo (Norway)[38] N=2,066 (18-65 years)		4.5%		
ICPE[39]		All: 3.9% F: 5.2% M: 2.7%		
NCS-Replication[40]			5.7%	3.1%
Midlife in the US Survey[41]				3.3%
GADIS[42] N=13,677				8.3%
NESARC[43] N=43,093 (Age>18 years)			All: 4.1% F:5.4% M:2.8%	All: 2.1% F:2.8% M:1.3%

	DSM III DIS Lifetime prevalence	DSM III R CIDI Lifetime prevalence	DSM IV CIDI Lifetime prevalence	DSM IV CIDI 12 month prevalence
Hong Kong[7] N=3,304 (15-60 years)				4.1%[1]
US _Primary Care N=1,029				10.1%
EDSP (Germany) [44] N=3,021 (14-24 years) *Baseline Results*			All: 0.8%	All: 0.5%
Bremer Jugenstudie (Germany)[45] N=1,935 (12-17 years)			0.4%	0.2%
Dresdener Studie (Germany)[46] N=3,021 (18-25 years)			2.4%	
TACOS (Germany)[47] N=4,075 (18-64 years)			0.8%	
NSMHW (Australia) [32 33] (N=10,641 >18 years				**3.1%**
ESEMed[48] N=21,425 (>18 years)			2.8%	1.0%
South Florida Study (USA)[49] N=1,803 (19-21 years)			1.4%	
GHS-MHS (Germany)[50] N=4,181 (18-65 years)				1.5%
Germany[51] N=7,124 (18-64 years)				1.5%
Morocco[52]				4.3% F: 91.1%
NZ[53] N=1,037				12%
Range	**7-31.1%**	**2.3-5.1%**	**0.4-5.7%**	**0.2-10.1%**

[1] 6 month prevalence

Co-morbidity

A New Zealand study found that of those followed from 1972 till 2005, 42% of those diagnosed with GAD, had co-morbid depression, where GAD preceded the depression.[53] They conclude that this comorbidity seemed to be associated with substantial health burden, as indicted by recurrent course, mental health service use and suicide attempt.

The ESEMeD study showed that patients with GAD were 32.7 times more likely to develop depression, 12.5 times more likely to have SAD and 1.5 times more likely to abuse alcohol (10.2 times more likely to be alcohol dependant).[54]

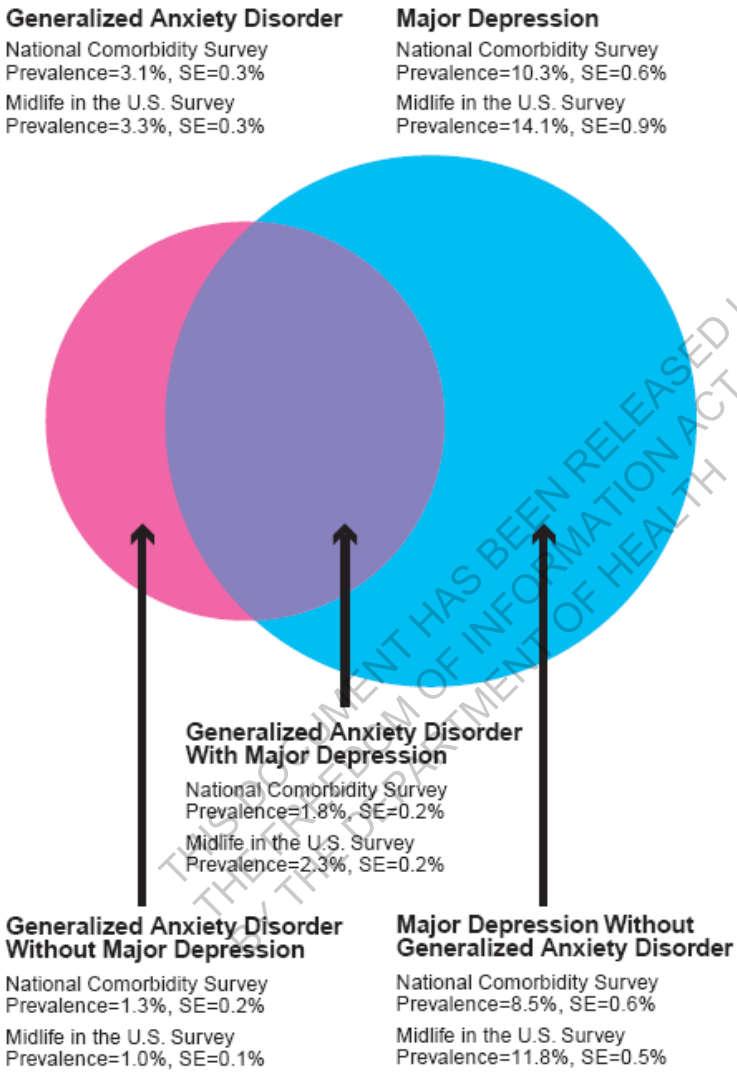
Table 4 Lifetime Co-morbidities with GAD

	Population	Any Co-morbidity		Major Depression		Agoraphobia		Alcholism		SAD	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
DSN-III											
LASA[36]	N=3,056 (55-85 years)			15%							
DSM-III-R											
NCS (USA)[3 55 56]	N=8,098 (15-54 years)	66.3%	90.4%	38.6%	62.4%	26.7%	25.7%	11.2%	37.6%	23.2%	34.4%
France	N=1,042 (18-65 years)	>60%		27.7%				25%			
DSM-IV											
NESARC[43]	General Age>18 years N=43,093	89.8%									
US -Primary Care[8]	N=1,029			69.7%				11.1%			
NZ[53]	General N=1,037				63-88%						
Germany[51]	18-64 years N=7,124	93.1%		70.6%							
NSMHW (Australia)[57]	**General N=10,641 >18 years**	**67.8%**		**44.9%**							
USA[51]	N=9,282 >18 years	85%									
GADIS[42]	GP N=13,677			4.2%							
ICPE Survey[39]	N=20,189		88.3%		60.9%		20.7%				34%
Range DSM IV		**66.3-**	**88.3-**	**4.2-70.6%**	**60.9-88%**	**26.7%**	**20.7-**	**11.1-25%**	**37.6%**	**23.2%**	**34-34.4%**

	Population	Any Co-morbidity		Major Depression		Agoraphobia		Alcholism		SAD	
		Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime
		93.1%	90.4%				25.7%				

Figure 3 shows the rate of comorbidities based on two studies and the overlap that exists.[41]

Figure 3 Prevalence and Comorbidity of Generalized Anxiety Disorder and Major Depression at 12 Months in Two National General Population Surveys[41]



Impact on Impairment

A central issue of debate is whether generalized anxiety is itself associated with impairment or disability, or whether the impairment in individuals with GAD is due entirely to other co-morbid disorders.[43] Epidemiological studies have addressed this question by assessing the comparative disability of GAD and major depressive episodes (MDE). In these studies[39 41] the separate and joint effects of GAD and MDE were evaluated by comparing the disability of pure GAD, pure MDE, and the two conditions when co-morbid. No significant differences in disability were found between pure GAD and pure MDE, and two of the three surveys found that individuals with co-morbid GAD-MDE had significantly greater disability than those with either pure GAD or pure MDE.

These findings have led researchers to conclude that the status of GAD as an independent disorder is at least as strongly supported as it is for MDE.[30 43]

It used to be thought that GAD, in the absence of other disorders, was associated with a low level of disability.[58] However, the chronic nature of GAD means that the condition imposes a substantial individual burden. This may manifest in the quality and level of functioning in social and occupational interactions, resulting in significant though indirect costs to society. This burden is most notable in terms of substantial impairments resulting in days where a sufferer is restricted from or unable to carry out daily activities, causing a reduction in the patient's quality of life and well-being.[10] The NCS and the "Midlife Development in the United States Survey" both state that the level of impairment related to GAD is considerable and equivalent to that of MD. [41] In fact, a combined analysis of these two surveys revealed that even GAD with no comorbidity is associated with marked impairments in psychosocial functioning equivalent to those caused by MD. [41]

A similar conclusion was arrived at in the analysis of the Australian NSMHWH. [57] In functional terms, persons with pure GAD had been unable to engage in their usual activities on an average of 6 days in the previous month, and their disability score on the SF-12 mental health scale fell more than one standard below the population average. **The authors conclude that the Australian data support that GAD, as a single disorder is**

significantly disabling. Consequently, the data supported that patients with GAD have a use of health services.

Diagnosis

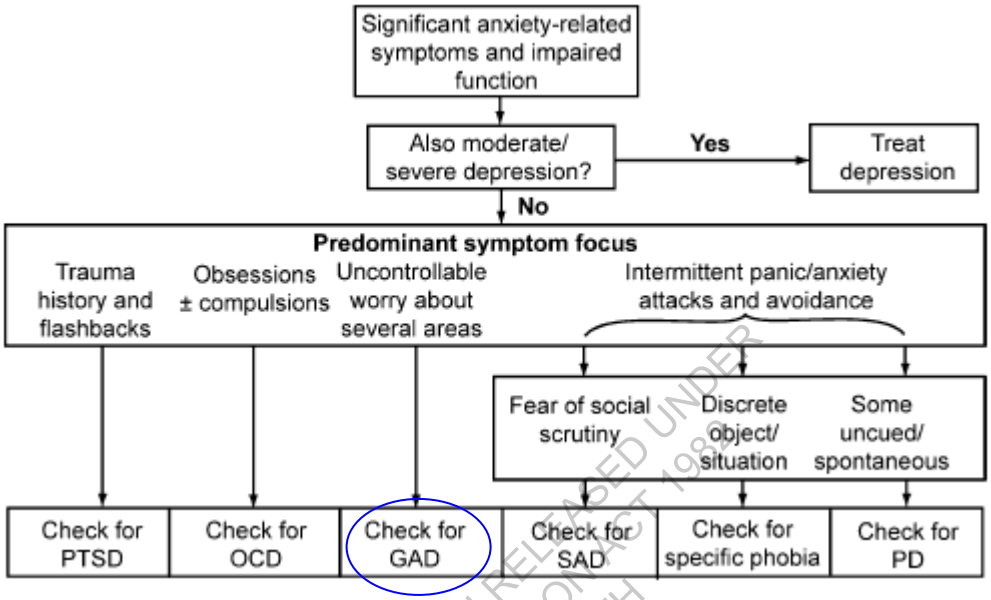
Some useful questions to ask in establishing a diagnosis of GAD[59]

- Are you a worrier?
- Do you think that you worry excessively?
- When things are going well do you still find things to worry about?
- Once you start to worry do you find it hard to stop?
- How much does worry interfere with your life?
- How long has worrying like this been a problem?

Excessive worry accompanied by significant symptoms of muscle tension, autonomic arousal and hypervigilance must be present for at least 6 months for a diagnosis of GAD to be made.

The following (Figure 4) depicts the latest diagnostic algorithm for exploring anxiety disorder issued by the British Association for Psychopharmacology:[60]

Figure 4 Diagnostic algorithm for exploring anxiety disorders[60]



Treatment

GAD follows a chronic course and may be either constant or fluctuating. Patients typically suffer symptoms for a number of years before being diagnosed and effectively treated, with retrospective studies suggesting symptoms may wax and wane for up to 20 years.[61-63] The Harvard/Brown Anxiety Research Program (HARP), a naturalistic, longitudinal study that assessed patients, with PD, PDA, SP, and GAD, at 6–12- month intervals for of 8 years, showed that the likelihood of these anxiety patients experiencing full remission was modest and more likely to occur during the first 2 years of the study. In addition, this study indicated that GAD patients continued remitting late into the study period.[64] This tends to support the idea of GAD having an episodic pattern in which periods of remission and recurrence are evident for many years.[65]

Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated a continued lack of treatment for many individuals with GAD.[43]

Approximately 50-59% of individuals with GAD received no treatment, [7] [43] with an average 2-year lag between onset and first treatment.[43]

A New Zealand study that followed a birth cohort to the age of 32 found that of the patients diagnosed as having pure GAD, 35% only had received mental health services and 19% psychiatric medication[66]. For patients with GAD and comorbid MDD these figures were higher with 57% accessing mental health services and 39% psychiatric medication.[66] Similar results were found in the ESEMeD study where for any anxiety around 36% of individuals had consulted any type of formal health services in the previous 12 months.[67] Overall approximately 30-39% of GAD patients receive appropriate treatment,[67] [58] [66] this was as low as 11% in the UK National Surveys of Psychiatric Morbidity.[68]

In summary, having examined all the evidence the data shows that 11-50% of patients diagnosed with GAD are treated.

The UK National Surveys of Psychiatric Morbidity study also identified that the factors influencing treatment with antidepressants are the number of psychiatric symptoms, marital status, age and employment status. It is clear that by far the strongest influence is that of symptomatic severity, with the most severe category over four times as likely as the least severe to receive antidepressants.[67]

There are a variety of agents that can be used to treat GAD. Figure 1 shows the onset of effect of different anxiolytic drugs (benzodiazepines, buspirone and antidepressants).[69] It can be seen that although benzodiazepines have a rapid anxiolytic effect (without onset worsening) there are major concerns surrounding long-term use of these. **Indeed some argue for the theory that antidepressants affect predominantly psychological symptoms whereas benzodiazepines affect predominantly somatic symptoms in patients with GAD.[70]**

Adverse effects on discontinuation with benzodiazepines are more frequent than with other drugs, and these may be caused by recurrence or rebound (recurrence with increased intensity) of the original anxiety symptoms, or by drug withdrawal effects.[71] [72] The benzodiazepine withdrawal syndrome is potentially serious, but is generally mild and self-limiting (up to 6 weeks). As a guide benzodiazepines may be used for 2–4 weeks to cover the onset worsening caused by some antidepressants, or on an occasional basis before exposure to a feared situation. [59] [60] [73] [74]

In order to assess the magnitude of the withdrawal syndrome some evidence is provided by a Canadian study which examined 30 consecutive inpatients admitted for assistance from their benzodiazepine detoxification.[75] These patients were long-term users of benzodiazepines (≥1 months, $\bar{x}$=86 months). Of all patients 20% were diagnosed with GAD. These patients were assessed as above therapeutic dose users. Another study assessed 131 long-term, therapeutic dose users (daily use >3 months; $\bar{x}$=3 years) who had entered an outpatient treatment program for discontinuations of benzodiazepines.[75] These patients tended to shift their use of medication from an as-prescribed to an as-needed pattern. The majority of patients (91%) had made at least one attempt to decrease their dose or stop their use of benzodiazepines, and all who had done so reported experiencing symptoms upon attempting to discontinuation. Of the patients admitted 33% had GAD.

Studies of the long-term efficacy of benzodiazepines have reported the development of tolerance or loss of effect over time in the treatment of anxiety. Additionally, a high relapse rate (65%) is observed in the 6-month period following benzodiazepine discontinuation after short-term treatment.[76]

Figure 5Onset of effect of different anxiolytic drugs[69]

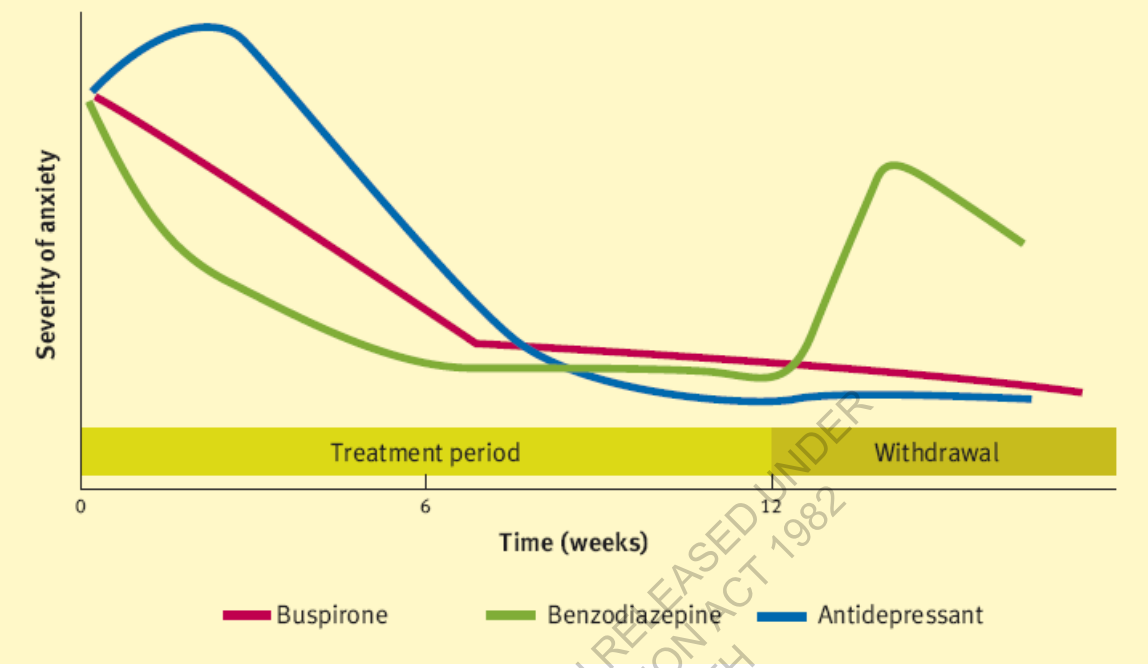


Table 5 Guidelines for Social Anxiety Disorder or Social Phobia

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
Recognition and diagnosis	Although generalized anxiety disorder (GAD) is amongst the most common mental disorders in primary care, and is associated with increased use of health services, it is often not recognized: possibly because only a minority of patients present with anxiety symptoms (most patients with present with physical symptoms), and doctors tend to overlook anxiety unless it is a presenting complaint . The disability associated with GAD is similar to that with major depression.[78] Patients with 'comorbid' depression and GAD have a more severe and prolonged course of illness and greater functional impairment,[41] and a greater chance of being recognized as having mental health problems, though not necessarily as having GAD[10 79].	Some of the symptoms associated with GAD are as follows (3 of these symptoms. Of at least moderate severity, should be present for a diagnosis): • Restlessness or feeling 'keyed up' or 'on edge' • Being easily fatigued • Difficulty concentrating or mind 'going blank' • Irritability • Muscle tension • Sleep disturbance (difficulty falling or staying asleep or restless unsatisfying sleep)	The accurate diagnosis of panic disorder or generalised anxiety disorder is central to the effective management of these conditions. It is acknowledged that frequently there are other conditions present, such as depression, that can make the presentation and diagnosis confusing. An algorithm has been developed to aid the clinician in the diagnostic process, and to identify which guideline is most appropriate to support the clinician in the management of the individual patient.
Acute Treatment	Systematic reviews and placebo-controlled RCTs indicate that some SSRIs (escitalopram, paroxetine and sertraline), the SNRI venlafaxine, some benzodiazepines (alprazolam and diazepam), the tricyclic imipramine, and the [5-HT.sub.1A] partial agonist buspirone are all efficacious in acute treatment. Other compounds with proven efficacy include the antipsychotic trifluoperazine, the antihistamine hydroxyzine, the anticonvulsant pregabalin, and the sigma-site ligand	• Treatment with benzopiazepine for up to 2 weeks followed by a gradual reduction of dose to zero within 6 weeks. Subsequent use should be on an 'as required basis'. • Diazepam 2-5mg orally up to twice a day or • Diazepam 5-10mg at night or • Oxazepam 15-30mg orally, as a single dose, up to twice a day	• support and information • problem solving • benzodiazepines 2-4 weeks • sedating antihistamines • self help Note level of evidence differs

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
	opipramol. Treatments with unproven efficacy in GAD include the beta-blocker. There have been few comparator-controlled studies, and most reveal no significant differences in efficacy between active compounds: however, escitalopram (20 mg/day) has been found significantly superior to paroxetine (20 mg/day), and venlafaxine (75-225 mg/day) superior to fluoxetine (20-60 mg/day) on some outcome measures in patients with comorbid GAD and major depression. Psychological symptoms of anxiety may respond better to antidepressant drugs than to benzodiazepines.		
Long-term treatment	Double-blind studies indicate that continuing with SSRI or SNRI treatment is associated with an increase in overall response rates: from 8 to 24 weeks with escitalopram or paroxetine; from 4 to 12 weeks with sertraline and from 8 to 24 weeks with venlafaxine. Placebo-controlled relapse-prevention studies in patients who have responded to previous acute treatment reveal a significant advantage for staying on active medication (escitalopram or paroxetine), compared to switching to placebo, for up to six months.	These should be nonpharmacological as pharmacological treatments have statistically significant, but clinically modest effects. Some agents used: • Venlafaxine • Buspirone • paroxetine	• psychological therapy – CBT, conditions apply • pharmacological therapy (antidepressant medication) • SSRIs should be offered • reviewed at 2, 4, 6 and 12 weeks • duration - 12 weeks • if not responding at 12 weeks switch to other SSRI, conditions apply • if responding at 12 weeks continue treatment for another 6 months • venlafaxine initiated only by specialist mental health practitioners, including GPs with a special interest in mental health • self-help

	British Guidelines[60 73]	Australian Guidelines[77]	NICE Guidelines[74]
			•
Comparative efficacy of pharmacological, psychological and combination treatments	Drug or psychological treatments, delivered singly, have broadly similar efficacy in acute treatment. Relapse rates are lower with cognitive behaviour therapy than with other forms of psychological treatment, but the comparative efficacy of drug and psychological approaches over the long term is not established. It is uncertain whether combining drug and psychological treatments is associated with greater overall efficacy than with either treatment, given alone.	Recommended primary treatments for GAD are nonpharmacological. Initial treatment should include listening to the patient, counselling and the teaching of relaxation techniques, personal and interpersonal strategies and coping skills.	• Cognitive and behavioural techniques combined had greater effect sizes than the individual interventions. • In the short term, cognitive and behavioural techniques were as effective as pharmacological therapies, but evidence is lacking for long term effectiveness. • The Gould meta-analysis found no difference in treatment outcomes for men and women.
When initial treatments prove unhelpful	There is no clear evidence for an increase in response with dose escalation after an initial non-response to a lower dose. Switching between treatments with proven efficacy may be helpful.		Switching to another SSRI
Duration of Treatment	12 weeks initial response, if responding at least another 6 months.		12 weeks initial response, if responding at least another 6 months.

Effects of Treatment with co-morbidities

For a full analysis of treatment with comorbid GAD refer to Attachment 8. Recent epidemiological data suggests that the impact of comorbidity in clinical outcomes is no greater in GAD than in other anxiety disorders.[80] Moreover, comorbidities such as major depression do not appear to change the course of GAD.[80] There are also data supporting the notion that psychotherapy may have an additional impact in the comorbid conditions associated with GAD.[81]

Epidemiologic studies have demonstrated the negative implications of comorbidity for course of illness.[82 83] Studies have found that the best predictors in cases of GAD and panic were severity and duration of symptoms, as well as comorbid depression. [15] The HARP study similarly found that the likelihood of remission of GAD and any other comorbid condition after one year was half the annual rate for GAD alone.[84] In a recent prospective study with nortriptyline or interpersonal psychotherapy, it was shown that while both treatments were effective, patients with comorbid GAD had a longer time to recovery.[85]

Evidence presented in this Attachment, regarding the impact of treatment in co-morbidities, is sparse and certainly does not meet Level 1 evidence. When pharmacotherapy is considered, upon examination of the two trials utilising escitalopram, it would seem that patients with at least one anxiety disorder and comorbid depression has a greater improvement in HAM-A score than those without comorbid anxiety. This would seem to indicated that at worst comorbid patients would respond similarly to those with pure depression and at best would show an improved outcome, when measured in terms of HAM-A. Response to both depression and anxiety has been shown in younger and elderly cohorts.

The conclusions from two open-label studies that examined patients with comorbidities are reported below: :[86 87]

a) The use of anxiolytics had no impact on the outcome

b) Of the 61% of patients experiencing a co-morbidity, results showed that anxiety symptoms as measured with the HAM-A, improved in parallel to the improvement in depressive symptoms, with escitalopram treatment.

c) Patients with at least one anxiety disorder had a greater improvement in HAM-A score than those without comorbid anxiety, but there was no statistically significant difference in the improvement in HAM-A scores as a function of baseline severity of depression, indicating that comorbid depression did not affect response to treatment of anxiety.

d) The remission rate for anxiety symptoms (38.1%) is very close to the 36% reported in a randomized, double-blind clinical trial of escitalopram in patients with pure GAD.[88] Patients with a comorbid anxiety disorder responded well to treatment, particularly those with GAD, SAD, or obsessive–compulsive disorder.

e) In a small study in elderly patients with comorbid GAD and MDD Escitalopram was associated with significant improvements in symptoms of anxiety and depression.

Treatment Outcomes

Like other mental disorders, the placebo response rate may range from 20% to over 50% and what contributes to this is not always clear from study reports.[74]

Hamilton Anxiety Scale (HAMA)

This scale rates the patient's level of anxiety based on feelings of anxiousness, tension and depression; any phobias, sleep disturbance, or difficulty in concentrating, the presence of genitourinary, cardiovascular, respiratory, autonomic or somatic symptoms, and the interviewer's assessment of the patient's appearance and behaviour during the interview are also rated.

The HAMA was developed to quantify the severity of symptoms of anxiety and is widely used to evaluate anxiety in clinical studies.

The Hamilton Anxiety Scale consists of 14 items, each defined by a series of symptoms; 1) anxious mood, 2) tension, 3) fears, 4) insomnia, 5) intellectual, 6) depressed mood, 7) somatic complaints: muscular, 8) somatic complaints: sensory, 9) cardiovascular symptoms, 10) respiratory symptoms, 11) gastrointestinal symptoms, 12) genitourinary symptoms, 13) autonomic symptoms, and 14) behaviour at interview.

Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (very severe). The sum (total score) indicates the severity of anxiety; less than 12 is normal, 18 mild anxiety (and the lowest threshold at which medication is usually prescribed), 25 moderate anxiety, and 30 severe anxiety.[89]

Typically in clinical trials response is determined for a ≥50% reduction in HAM-A and remission is defined by patients with a HAM-A<10 or a HAM-A<8[90], both of which is within the range of normal anxiety as determined by HAM-A<12.[89]

Consensus conferences proposed that for GAD, remission is defined as HAM-A≤7-10 functional impairment is SDS≤1 on each item and a HAM-D score of ≤7.[91 92]

HAMA Psychic Anxiety Subscale

The HAMA psychic anxiety subscale is derived from the HAMA scale and consists of the sum of the following items: item 1 (anxious mood), item 2 (tension), item 3 (fears), item 4 (insomnia), item 5 (intellectual), item 6 (depressed mood), and item 14 (behaviour at the interview).

HAMA Somatic Anxiety Subscale

The HAMA somatic anxiety subscale is derived from the HAMA scale and consists of the sum of the following items: item 7 (somatic, muscular), item 8 (somatic, sensory),

item 9 (cardiovascular), item 10 (respiratory), item 11 (gastrointestinal), item 12 (genitourinary) and item 13 (other autonomic symptoms).

Hamilton Depression Rating Scale

This 17-item scale rated the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety (psychic and somatic), and agitation; level of insight; patterns of insomnia (early, middle, late); loss of interest in work and other activities; weight loss, hypochondriasis psychomotor retardation; genital symptoms, gastrointestinal somatic symptoms and general somatic symptoms. Each item was scored on 3-, 4- or 5-point scale with 0 reflecting no symptoms and higher scores reflecting increasing symptom severity.

(Source: SCT-MD-05 Study Report p. 16)

Hospital Anxiety and Depression Scale (HAD)

The HAD scale is completed by the patient and comprises two subscales: one which measures depression (D-scale) and one which measures anxiety (A-scale). Each subscale consists of seven items, with four possible response alternatives (scored from 0 to 3, with 0 reflecting the most enjoyment/least anxiety). The D-scale consists of HAD items 1, 3, 5, 8, 10, 11 and 13, and the A-scale consists of HAD items 2, 4, 6, 7, 9, 12 and 14. Patients fill in the scores that most accurately reflect the way they had felt over the previous days. Scores for the depression and anxiety subscales are calculated separately.

(Source: Study Report for 99815 p.33)

Clinical Global Impression (CGI)

The CGI[93] are categorical scales used as both primary (though they are not recommended as primary and are most useful as secondary scales to help judge the clinical relevance of the finding) and secondary efficacy scales and as categorical scales to define responders.[90] CGI consists of two subscales:

- Clinical Global Impressions – Improvement scale (CGI-I):
  This scale evaluates a patient's total improvement from baseline I on a 7 point-scale, regardless of whether the improvement is related to the study product. The assessor rates the patient from 1 (very much improved) to 7 (very much worse)
- Clinical Global Impressions – Severity scale (CGI-S):
  This scale evaluates a patient's severity of disease on a 7-point scale based on the investigators total clinical experience with this population. The assessor rates the patient from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

Responders and Remitters on the CGI scale are classified as:

Responders: CGI-I≤ 2 (much or very much improved)[90] or CGI-I ≥50% reduction[94]. These patients have improved but are usually not considered as having reached remission.

Remission:[90] CGI-S≤ 2 (normal, not at all ill, or borderline illness). This has been used to define remitters but the level of remission represented by these scores remains controversial.

Quality of Life Questionnaire (QOL)

This 16-item patient-rated questionnaire is derived from the Quality of Life, Enjoyment, and Satisfaction Questionnaire. Patients answered questions based on their satisfaction during the previous two weeks regarding mood, health, activities of daily living, and interpersonal relationships on a 5-point scale. Unlike the other efficacy ratings, higher scores on this scale reflect improved function.
(Source: SCT-MD-05 Study Report p. 16)

Sheehan Disability Scale (SDS)

The SDS[1] is a 3-item scale to measure impairment. The items address the impact of symptoms of SAD on work, social life, and family life, within the last 7 days. The rating

is based up an interview with the patient. This scale may also be helpful in indicating the relevance of improvement. It has been shown to be efficient in demonstrating significant differences in improvement in function from the patients' perspective. Since GAD is associated with considerable impairment of function the SDS may provide a useful comment on the functional relevance of the treatment.[90]

Duration of Treatment

Acute Treatment: 12 weeks**,** this is also the period required to determine efficacy of a medication aiming to treat GAD.[60 74]

Long –Term Treatment: for patients responding at 12 weeks, an additional 6 months, at least**,** is recommended.[60 74]

Defining Response and Remission

When defining 'response' to a treatment on a standard rating scale, a score which equates to ≥50% reduction on the scale has been found to be too conservative, with a clinically measurable difference being seen at a smaller reduction from baseline as can be seen in Table 6.

Table 6 Correlation of Response/Treatment Between Scales[94]

CGI Defined	Corresponding Reductions		
	MADRS	HAM-A	LSAS
Response CGI-I ≥50% reduction	≥39%	≥42%	≥31%
Remission CGI-S ≤2	≤11 points	≤ 9points	≤36 points

The HAM-A of ≤ 9points full well within the range arrived at the consensus conferences.[91 92]

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