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2 December 2022

s 9(2)(a)

By email: s 9(2)(a)
Ref: H2022016268

Dear s 9(2)(a)

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) to Manatū Hauora (the Ministry of Health) on 4 November 2022 for:

> *"Please provide the last approved labels, data sheets and CMIs for*
> *1. Aricept Film Coated Tablets, donepezil hydrochloride 10 mg & 5 mg, TT50-5907 and -5907a.*
> *2. Cipralex Film Coated Tablets, escitalopram oxalate 5 mg, 10 mg, 15 mg & 20 mg, TT50-6777, -6777a, -6777b & -6777c."*

Four documents have been identified within scope of your request. These are itemised in Appendix One to this letter, and copies of the documents are enclosed. Where information is withheld under section 9 of the Act, I have considered the countervailing public interest in releasing information and consider that it does not outweigh the need to withhold at this time.

I trust this information fulfils your request. Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Manatū Hauora website at: www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests.

Yours sincerely

Chris James
Group Manager
Medsafe

Appendix 1: List of documents for release

#	Date	Document details	Decision on release
1	24 October 2002	Cipralex approved Data Sheet	Released in full
2	2 October 2002	Cipralex (5mg, 10mg, 15 mg & 20mg) approved labels	Some information withheld under section 9(2)(b)(ii) of the Act, where its release would likely unreasonably prejudice the commercial position of the person who supplied the information.
3	N/A	Aricept (5mg &10mg) approved abels	Released in full
4	10 October 2022	Cipralex approved CMI	

Document 1

DATA SHEET

CIPRALEX

NAME OF THE DRUG:

Escitalopram oxalate

Chemical name:

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

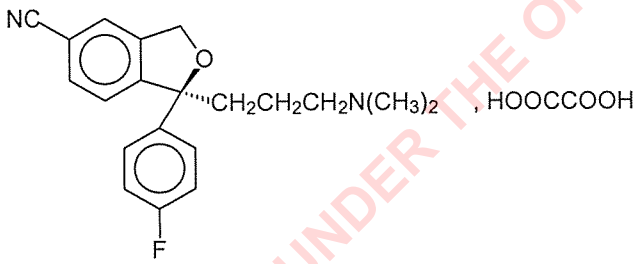
Chemical Abstracts No.

219861-08-2

Molecular weight

$C_{20}H_{21}FN_2O$, $C_2H_2O_4$: 414.42

Structural formula:



DESCRIPTION:

Escitalopram is the active 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.

Excipients in CIPRALEX: cellulose-microcrystalline, silica - colloidal anhydrous, talc, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

PHARMACOLOGY:

Pharmacodynamics

Biochemical and behavioural studies have shown that escitalopram is a potent inhibitor of serotonin (5-HT)-uptake (in vitro IC_{50} 2nM). The inhibition of 5-HT uptake is the only recognised mechanism of action of escitalopram capable of explaining the pharmacological and clinical effects of escitalopram.

On the basis of *in vitro* studies, escitalopram is the most selective Serotonin Reuptake Inhibitor yet developed with no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminiobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the SSRI's, 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.

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 re-uptake than escitalopram *in vitro*. It is therefore unlikely to contribute significantly to the overall antidepressant effect.

Pharmacokinetics

Absorption

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.

Excretion

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. 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.

Elderly patients (>65 years)

A longer half-life and decreased clearance values, due to a reduced rate of metabolism, have been demonstrated in the elderly.

Reduced hepatic function

There is no data on the use of escitalopram in reduced hepatic function. However, based on data for racemic citalopram, escitalopam is expected to be eliminated more slowly in patients with reduced hepatic function. The half-life of escitalopam is expected to be about twice as long and steady state escitalopam concentrations at a given dose will be about twice as high as in patients with normal liver function.

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. Escitalopam 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).

Polymorphism

Based on *in vitro* results with escitalopram and *in vivo* results with the racemic citalopram, genetic polymorphism with respect to CYP2D6 and CYP2C19 is considered of no clinical relevance. Therefore, there is no need for individualised dosing based on these phenotypes.

CLINICAL TRIALS:

Two fixed dose studies and one flexible dose study has 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 populations studied were therefore defined as suffering from moderate to severe depression. 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). Both ranges are comparable to those reported for development programmes with other SSRIs. The magnitude of the difference is larger with escitalopram than with citalopram.

In the study with two parallel escitalopram dose groups, analysis of subgroups of patients showed a trend toward greater improvement in patients with severe major depressive disorder (HAMD >25) receiving 20 mg/day as compared to 10 mg/day.

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 (HAMA) and the anxiety factor of the Hamilton Depression Rating Scale (HAMD scale) were used, results have shown that escitalopram was better than placebo.

Two relapse prevention or maintenance studies of 24 weeks´ duration have been carried out with the racemate. In both studies the racemate showed reduced relapse hazard rates and prolonged time to relapse compared to placebo.

Two placebo-controlled, parallel group studies with the racemate, including one in the elderly, addressed recurrence prevention over a 1 to 2 year recurrence prevention phase. In both patient populations, the racemate led to prolonged time to recurrence in all dose groups compared to placebo.

Although comparative studies have not yet been completed with escitalopram versus tri-/tetracyclic antidepressants or other SSRIs, data with the racemate demonstrate therapeutic efficacy comparable to other SSRIs in the treatment of major depression.

Document 1

INDICATIONS:

Treatment of major depression.

CONTRAINDICATIONS:

Hypersensitivity to citalopram and any excipients in Cipralex (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 Drugs). Some cases presented with features resembling serotonin syndrome (see Adverse Reactions).

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 7 days should elapse after discontinuing escitalopram treatment before starting a MAOI or RIMA.

PRECAUTIONS:

Haemorrhage - There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), as well as in patients with a history of bleeding disorders.

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), 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.

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.

Suicide - As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is

achieved. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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 advisable.

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 - After prolonged administration abrupt cessation of SSRIs may produce withdrawal reactions in some patients. Although withdrawal reactions may occur on stopping therapy, the available preclinical and clinical evidence does not suggest that SSRIs cause dependence.

Withdrawal reactions have not been systematically evaluated with escitalopram. However, limited withdrawal reactions have been observed with the racemic citalopram; dizziness, headache and nausea.

The withdrawal reactions are mild and self-limiting. It is recommended that treatment should be tapered gradually on discontinuation.

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.

Preclinical Safety. High doses of escitalopram, which resulted in plasma C_{max} for escitalopram and metabolites at least 10-fold greater than anticipated clinically, have been associated with convulsions and ECG abnormalities in experimental animals.

Carcinogenicity, mutagenicity and impairment of fertility. No carcinogenicity, mutagenicity or impairment of fertility studies were performed with escitalopram. However, other preclinical 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 80mg/kg/day, respectively.

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

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. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn infant.

Oral treatment of rats with escitalopram during organogenesis at maternotoxic doses led to increased post-implantation loss and reduced fetal 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 was 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.

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 these data support the safety of use of citalopram in breastfeeding women, the decision to breast feed should always be made as an individual risk:benefit analysis.

Interaction with other drugs:

Co-administration with MAO inhibitors may cause serotonin syndrome (see Contra indications).

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.

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.

Escitalopram has a low potential for clinically significant drug interactions. I*n 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 3A, 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 racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) resulted in increased plasma concentrations of the racemate (<45% increase). Thus, caution should be exercised at the upper end of the dose range of escitalopram when used concomitantly with high doses of cimetidine.

Effects of escitalopram on other drugs in vivo

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 clinical important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

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

ADVERSE REACTIONS:

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.

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

Figures marked with * in below table indicate adverse reactions (incidence with escitalopram statistically significantly different from placebo (P<0.05))

System Organ Class & Preferred Term	PLACEBO n (%)	ESCITALOPRAM n (%)
Patients Treated	592	715
Patients with Treatment Emergent Adverse Event	379 (64.0)	520 (72.7)
GASTRO-INTESTINAL SYSTEM DISORDERS		
nausea	44 (7.4)	107 (15.0) *
diarrhoea	31 (5.2)	57 (8.0) *
mouth dry	27 (4.6)	44 (6.2)
dyspepsia	19 (3.2)	31 (4.3)
constipation	6 (1.0)	25 (3.5) *
abdominal pain	16 (2.7)	21 (2.9)
gastroenteritis	4 (0.7)	11 (1.5)
vomiting	13 (2.2)	11 (1.5)
flatulence	4 (0.7)	9 (1.3)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
headache	97 (16.4)	113 (15.8)
dizziness	21 (3.5)	43 (6.0) *
paraesthesia	4 (0.7)	11 (1.5)
migraine	8 (1.4)	10 (1.4)
tremor	4 (0.7)	10 (1.4)
vertigo	5 (0.8)	10 (1.4)
PSYCHIATRIC DISORDERS		
insomnia	23 (3.9)	66 (9.2) *
somnolence	13 (2.2)	49 (6.9) *
anorexia	5 (0.8)	21 (2.9) *
libido decreased	4 (0.7)	18 (2.5) *
anxiety	12 (2.0)	15 (2.1)
appetite increased	8 (1.4)	12 (1.7)
agitation	4 (0.7)	11 (1.5)
nervousness	7 (1.2)	11 (1.5)
dreaming abnormal	7 (1.2)	10 (1.4)
impotence [gs]		6 (2.7) *
RESPIRATORY SYSTEM DISORDERS		
upper respiratory tract infection	41 (6.9)	44 (6.2)
rhinitis	30 (5.1)	35 (4.9)
sinusitis	13 (2.2)	31 (4.3) *
pharyngitis	18 (3.0)	20 (2.8)
yawning	1 (0.2)	11 (1.5) *

bronchitis	14 (2.4)	10 (1.4)
BODY AS A WHOLE - GENERAL DISORDERS		
influenza-like symptoms	24 (4.1)	36 (5.0)
fatigue	15 (2.5)	34 (4.8) *
back pain	30 (5.1)	22 (3.1)
hot flushes	3 (0.5)	10 (1.4)
fever		9 (1.3) *
leg pain	3 (0.5)	8 (1.1)
pain	6 (1.0)	7 (1.0)
SKIN AND APPENDAGES DISORDERS		
sweating increased	10 (1.7)	34 (4.8) *
MUSCULO-SKELETAL SYSTEM DISORDERS		
arthralgia	3 (0.5)	11 (1.5)
myalgia	8 (1.4)	9 (1.3)
skeletal pain	6 (1.0)	9 (1.3)
REPRODUCTIVE DISORDERS, FEMALE		
anorgasmia [gs]	1 (0.2)	10 (2.0) *
METABOLIC AND NUTRITIONAL DISORDERS		
weight increase	9 (1.5)	13 (1.8)
RESISTANCE MECHANISM DISORDERS		
herpes simplex	2 (0.3)	8 (1.1)
REPRODUCTIVE DISORDERS, MALE		
ejaculation disorder [gs]	-	21 (9.3) *
VISION DISORDERS		
vision abnormal	4 (0.7)	10 (1.4)
conjunctivitis	5 (0.8)	7 (1.0)
HEART RATE AND RHYTHM DISORDERS		
palpitation	7 (1.2)	10 (1.4)
SECONDARY TERMS		
inflicted injury	9 (1.5)	9 (1.3)

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

The following adverse reactions have been observed with escitalopram at an incidence of < 1%:

Nervous system disorders – taste disturbance, sleep disorder

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).

Gastrointestinal disorders - dry mouth.

General disorders - allergic reactions.

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

Psychiatric disorders – agitation.

Skin disorders - ecchymoses, pruritus, angioedema, purpura.

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

Disorders of the eye – abnormal vision

Gastrointestinal disorders – vomiting

Hepato-biliary disorders – abnormal liver function tests

Musculoskeletal disorders – arthralgia, myalgia

Neurological disorders - seizures, tremor, movement disorders.

Psychiatric disorders – hallucinations, mania, confusion, anxiety, depersonalisation, panic attacks, nervousness.

Renal and Urinary Disorders – urinary retention

Reproductive disorders – galactorrhoea.

Skin disorders – rash, ecchymoses, pruritus, angioedema.

DOSAGE AND ADMINISTRATION

Adults

Cipralex should be administered as a single oral dose of 10 mg daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg 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.

When stopping SSRI therapy gradual dose reduction should be considered.

Elderly patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly, therefore a lower maximum dose should be considered.

Children

Not recommended, since safety and efficacy have not been established in this population.

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.).

Reduced hepatic function

Dosages should be restricted to the lower end of the dose range in patients with hepatic insufficiency (group A and B according to modified Child –Turcotte´s score system).

OVERDOSAGE:

Symptoms

Doses of 190 mg have been taken without any symptoms being reported. Furthermore, no symptoms were reported after intake of 600 mg (dose not confirmed).

Treatment

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal should be given as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

PHARMACEUTICAL CONSIDERATIONS

Cipralex tablets have a shelf life of two years. Store below 30°C.

MEDICINES CLASSIFICATION

Prescription Medicine

PRESENTATION:

Film-coated tablets in packs of 28 tablets.

Description of tablets

5 mg: Round, white, film-coated tablets marked with "EK" on one side.

10 mg: Oval, white, scored , film-coated tablets marked with "EL" on one side.

15 mg: Oval, white, scored, film-coated tablets marked with "EM" on one side.

20 mg: Oval, white, scored, film-coated tablets marked with "EN" on one side.

MANUFACTURED BY:

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Date of preparation: 10 October 2002.
Medsafe Approval: 24 October 2002.

s 9(2)(b)(ii)

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Document 2

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Document 2

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Document 2

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[redacted]

s 9(2)(b)(ii)

[redacted]

Document 2

s 9(2)(b)(ii)

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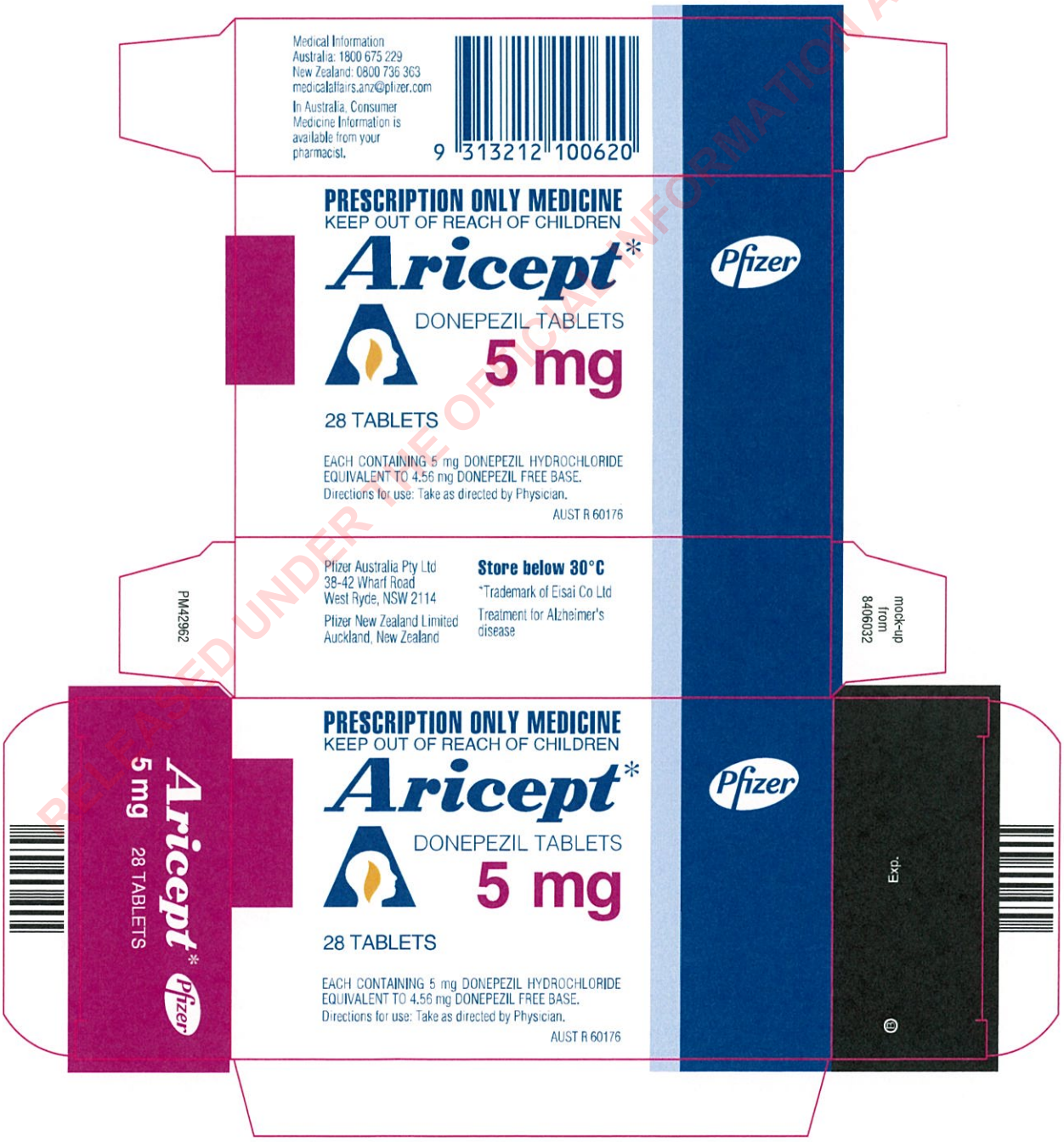
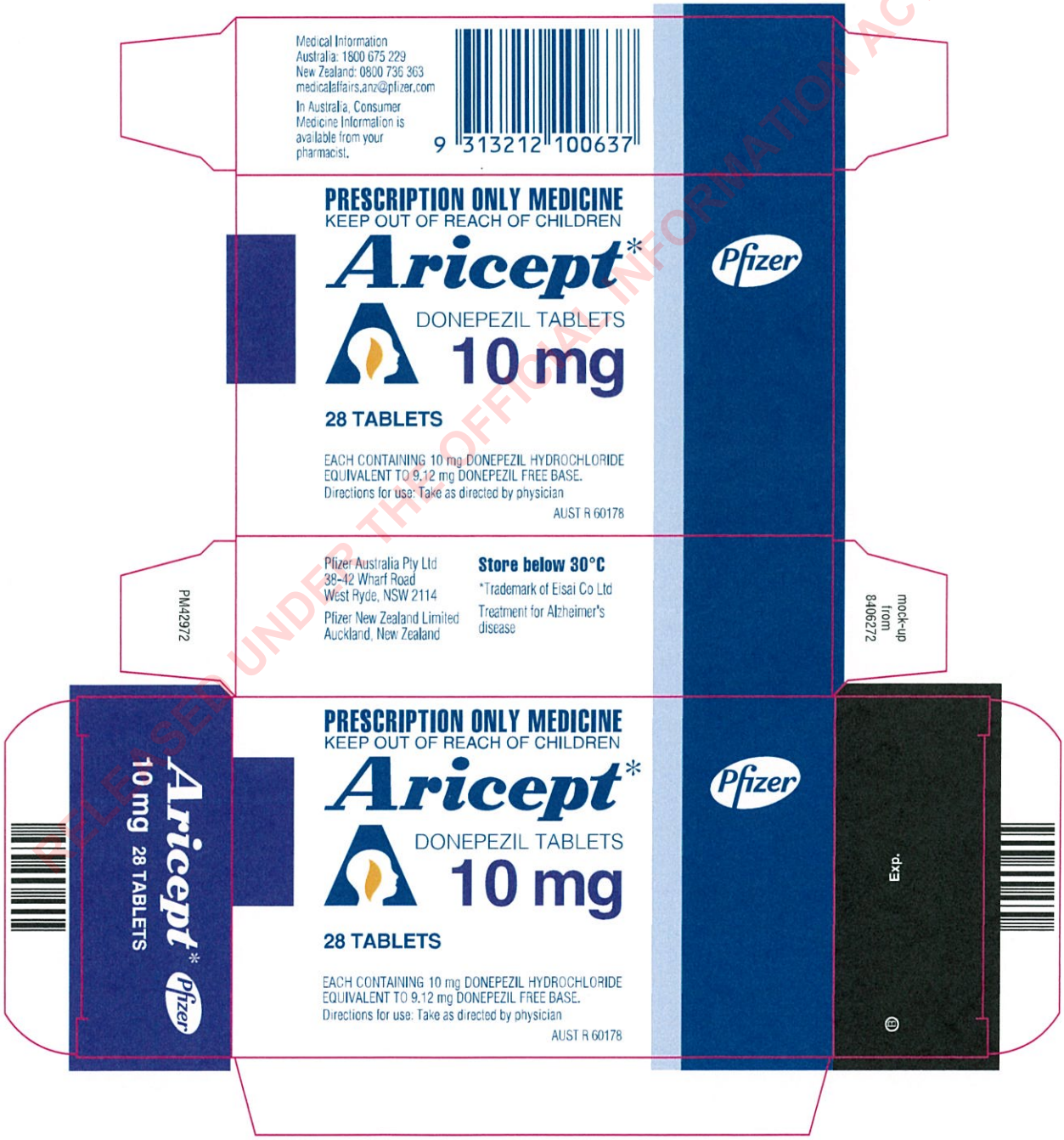
Document 3

Proposed Aricept 5 mg Carton Label



Proposed Aricept 10 mg Carton Label

Document 3



Document 4

CIPRALEX

Escitalopram oxalate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about **CIPRALEX**. It does not contain all the information that is known about **CIPRALEX**.

It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you using **CIPRALEX** against the benefits they expect it will have for you.

If you have any concerns about using this medicine ask your doctor or pharmacist.

Keep this leaflet with the medicine. You may need to read it again.

What CIPRALEX is used for

CIPRALEX is a Selective Serotonin Reuptake Inhibitor (SSRI) and belongs to a group of medicines known as antidepressants. These medicines help to normalize the levels of serotonin in the brain. Disturbances in the serotonin system of the brain are key factors in the development of depression and related disorders.

CIPRALEX is used for the treatment of depression. This disease is characterized by low/depressed mood, lack of energy, melancholia, feelings of little or no worth, sleeping disorders, withdrawal and being unable to cope with daily tasks. Depression may also be accompanied by suicidal thoughts. Depressed patients may further suffer from symptoms of anxiety.

Cipralex will relieve these symptoms and make you feel better.

Your doctor, however, may prescribe **CIPRALEX** for another purpose. Ask your doctor if you have any questions about why **CIPRALEX** has been prescribed for you.

Before you take CIPRALEX

When you must not take it.

Do not take CIPRALEX if you have ever had an allergic reaction to CIPRALEX or any of the ingredients listed at the end of this leaflet.
If you have an allergic reaction you may get a skin rash, have difficulty in breathing, get symptoms of hayfever or feel faint.

CIPRALEX should not be taken at the same time as taking medication known as monoamine oxidase inhibitors (MAOIs), such as phenelzine and tranylcypromine and moclobemide which are also used for the treatment of depression, and selegiline, which is used for the treatment of Parkinson´s disease.

One day must elapse after you have finished taking moclobemide before you start taking your **CIPRALEX** tablets. If you have taken any other MAOI you will need to wait 14 days. After stopping Cipralex you must allow 7 days before taking any MAOI.

The herbal remedy St John's wort (Hypericum perforatum) should not be taken at the same time as this medicine.

Do not take CIPRALEX after the expiry date (EXP) printed on the pack.
It may have no effect at all or, an entirely unexpected effect if you take it after the expiry date.

Do not take CIPRALEX if the packaging is torn or shows signs of having been tampered with.

Do not take CIPRALEX to treat any other complaints unless your doctor has instructed you to do so.

Before you start to take it

Your doctor must know about all the following before you start to take **CIPRALEX.**

You must tell your doctor if:

1. **you are allergic to any other medicines or any foods, dyes or preservatives.**

2. **you have any medical conditions, including:**

   heart disease
   epilepsy
   liver disease
   kidney disease
   diabetes
   manic depression
   bleeding tendency

   Your doctor will take the necessary precautions to ensure safe use of **CIPRALEX** if you have any of these medical conditions.

3. **you are taking any other medicines, including medicines that you buy without a prescription from a pharmacy, supermarket or health food shop.**
   Some of the medicines in common use that may interfere with **CIPRALEX** include cimetidine, sumatriptan (Imigran), lithium, tricyclic antidepressants (eg imipramine, desipramine), tramadol and tryptophan. You may need to take different amounts of your medicine or you may need to take different medicines.

   Your doctor or pharmacist can tell you what to do if you are taking this or any other medicines.

4. **you are pregnant or plan to become pregnant.**

   Do not take CIPRALEX if you are pregnant or breastfeeding unless you and your doctor have discussed the risks and benefits involved.
   It is not recommended that you do breastfeed while taking **CIPRALEX** as it is excreted in breast milk.

   If you have not told your doctor about any of these things, tell them before you take **CIPRALEX.**

5. **you have heart disease.** **CIPRALEX** may decrease your heart rate

Document 4

Use in children

Do not give CIPRALEX to children

CIPRALEX is not recommended for children as there is no specific information about such use. Always ask your doctor before giving medicines to children.

Use in elderly

CIPRALEX can be given to elderly patients. The effects of **CIPRALEX** in elderly patients are similar to that in other patients.

How to take CIPRALEX

How much to take

Your doctor will tell you how much CIPRALEX to take. Take the amount your doctor tells you to.

The usual dose is 10 mg per day. This may be increased by your doctor. The recommended maximum dose is 20 mg per day.

How to take it

Take **CIPRALEX** as a single dose either in the morning or in the evening. **CIPRALEX** may be taken with or without food.

It is best if the tablet is swallowed whole with a drink of water. Do not chew the tablets.

What to expect

As with other medicines for the treatment of depression it may take a few weeks before you feel any improvement. Therefore you should continue to take Cipralex even if it takes some time before you feel any improvement in your condition.

Individuals will vary greatly in their response to **CIPRALEX.** Your doctor will check your progress at regular intervals.

How long to take it

The duration of treatment may vary for each individual, but is usually at least 6 months. In some cases the doctor may decide that longer treatment is necessary. You should continue to take the tablets for as long as your doctor recommends, even if you begin to feel better. The underlying illness may persist for a long time and if you stop your treatment too soon, your symptoms may return.

When finishing a course

Abrupt cessation of this kind of medication may cause discontinuation symptoms such as dizziness, nausea and headache. **When you have completed your course of treatment it is therefore advised that the dose of CIPRALEX is gradually reduced over a couple of weeks**

If you forget to take it

If you miss a dose and remember in **less than 12 hours**, take it straight away, then continue as normal the next day. Otherwise, skip that day's dose but be sure to take the next day's dose when it is due.

Do not try to make up for missed doses by taking more than one dose at a time.
If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (Overdose)

Immediately telephone your doctor or Poisons Information Centre for advice, or go to casualty at your nearest hospital if you think that you or anyone else may have taken too much CIPRALEX . Do this even if there are no signs of discomfort or poisoning. Keep telephone numbers for these places handy.

Symptoms of overdosage may include:

- nausea (feeling sick)
- vomiting
- sweating
- drowsiness
- blue discolouration of the skin
- convulsions
- unconsciousness
- fast heart beats
- tremor

While you are taking CIPRALEX

Things you must do

Take CIPRALEX exactly as your doctor has prescribed.

If you do not follow your doctor's instructions, you may not get relief from your depression.
Try not to miss any doses and continue to take the medicine even if you feel well.

Tell your doctor immediately if you become pregnant while taking CIPRALEX.

Tell all doctors, dentists and pharmacists who are treating you that you are using CIPRALEX, especially if you are being started on any new medicines.

Things you must not do

Do not give this medicine to anyone else even if their symptoms seem similar to yours.

Things to be aware of

As with any new medicines you should take care when driving, operating machinery or drinking alcohol until you know how **CIPRALEX** affects you.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking CIPRALEX.

CIPRALEX helps most people with depression, but it may have unwanted side effects in some people.

All medicines have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.

The side effects of **CIPRALEX** are, in general, mild and disappear after a short period of time.

Tell your doctor if you notice any of the following and they worry you:

- Sinusitis (clogged or running nose)
- Decreased appetite
- Difficulties falling asleep
- Feeling sleepy
- Dizziness
- Yawning
- Nausea
- Diarrhoea
- Constipation
- Increased sweating
- Sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties getting orgasm)
- Fatigue
- Fever

Less frequent side effects may include:

- Disturbed sleep
- Taste disturbance

In addition a number of rare side-effects are known to occur with drugs that work in a similar way to Cipralex). These are:

- Dizziness when you stand up due to low blood pressure
- Decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused)
- Blurring of vision
- Vomiting
- Dry mouth
- Abnormal liver function test (increased amounts of liver enzymes in the blood)
- Pains in muscles and joints
- High fever, agitation, confusion, trembling and abrupt contractions of muscles may be signs of a rare condition called serotonin syndrome
- Seizures, tremors, movement disorders (involuntary movements of the muscles)
- Hallucinations, mania, confusion, panic attacks, depersonalisation, anxiety, nervousness, agitation
- Difficulties urinating
- Flow of milk in women that are not nursing
- Rash, increased tendency to develop bruises, itchings, patches of circumscribed swellings

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may get other side effects while using **CIPRALEX.**

There is no evidence that **CIPRALEX** is addictive, **however, if you suddenly stop taking CIPRALEX, you may get side effects. Tell your doctor if you get any side effects after stopping CIPRALEX.**

After taking CIPRALEX

Storage

CIPRALEX has a shelf life of 2 years.

Keep CIPRALEX in a cool place where the temperature stays below 30°C.

Keep CIPRALEX in the blister pack until it is time to take them.

Do not freeze CIPRALEX.
Do not leave CIPRALEX in the car on hot days.

Keep CIPRALEX away from direct sunlight.

Do not store CIPRALEX or any other medicine in the bathroom or near a sink or stove.
Heat, light and dampness can destroy some medicines.

Keep CIPRALEX where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above ground is a good place to store medicines.

Disposal

Dispose of the tablets where children cannot reach them.

Ask your pharmacist what to do with any CIPRALEX you may have left over if your doctor tells you to stop using it, or you find that the tablets have passed the expiry date.

CIPRALEX description

What CIPRALEX looks like

CIPRALEX is presented as 5mg, 10mg, 15mg & 20mg tablets and is available in packs of 28 tablets. The tablets are described below.

5 mg: Round, white biconvex film-coated tablets marked with "EK" on one side.

10 mg: Oval, white film-coated tablets. The tablets are scored and marked with "E" and "L" on each side of the score on one side of the tablet.

15 mg: Oval, white film-coated tablets. The tablets are scored and marked with "E" and "M" on each side of the score on one side of the tablet.

20 mg: Oval, white film-coated tablets. The tablets are scored and marked with "E" and "N" on each side of the score on one side of the tablet.

Ingredients

Each **CIPRALEX** tablet contains either 5mg, 10mg, 15mg or 20mg escitalopram (as oxalate salt).

CIPRALEX tablets also contain:
. cellulose – microcrystalline
. colloidal silica
. talc
. croscarmellose sodium
. magnesium stearate
. hypromellose
. macrogol
. titanium dioxide

Manufacturer

CIPRALEX is made in Denmark and supplied:

in Australia by:
Lundbeck Australia Pty Ltd
1/10 Inglewood Place
Norwest Business Park
Baulkham Hills NSW 2153
Ph: +61 2 9836 1655

in New Zealand by:
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