PROFESSIONAL INFORMATION

SCHEDULING STATUS **S5**

1 NAME OF THE MEDICINE

FICALI 5 film-coated tablets
FICALI 10 film-coated tablets
FICALI 15 film-coated tablets
FICALI 20 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Escitalopram oxalate corresponding to 5 mg, 10 mg, 15 mg or 20 mg escitalopram. Sugar free.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
FICALI 5: A 5,5 mm normal convex, white film-coated tablet debossed "EC" on one side and "G" on the other.
FICALI 10: A 9,5 mm x 5,5 mm oblong normal convex, white film- coated tablet debossed "EC½10" on one side and "G" on the other.
FICALI 15: A 10,5 mm x 6 mm ellipse normal convex, white film- coated tablet debossed "EC½15" on one side and "G" on the other.
FICALI 20: A 12,5 mm x 7 mm oblong normal convex, white film- coated tablet debossed "EC½20" on one side and "G" on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

4.2 Posology and method of administration

Posology
Adults:
Major Depressive episodes:
FICALI should be administered as a single oral dose of 10 mg daily in otherwise healthy adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.
Usually 2-4 weeks are necessary to obtain antidepressant response.
Elderly patients (> 65 years of age):
A longer half-life and a decreased clearance have been demonstrated in the elderly, therefore a lower initial and maximum dose should be considered.
Reduced renal function:
Dosage adjustment is not necessary in patients with mild to moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min) (see WARNINGS).
Reduced hepatic function:
Dosages should be halved to the lower end of the dose range in patients with hepatic insufficiency. When stopping FICALI therapy, gradual dose reduction should be considered. FICALI is administered as a single daily dose.
Serotonin withdrawal:
When stopping FICALI therapy, gradual dose reduction should be considered.
Method of administration
For oral use.
FICALI may be taken without regard to food intake.

4.3 Contraindications

- Hypersensitivity to escitalopram or to any of the excipients of FICALI (see section 6.1).
- Children under18 years of age; as safety and efficacy have not been established in this population.

Monoamine Oxidase Inhibitors:
Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on an MAOI (see section 4.5). Some cases presented with features resembling serotonin syndrome (see section 4.4 Class reactions). FICALI should not be used in combination with an MAOI.

FICALI may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing FICALI treatment before starting an MAOI.

4.4 Special warnings and precautions for use

Mania
FICALI should be discontinued in any patient entering a manic phase. FICALI should be used with caution in patients with a history of mania/hypomania.
Paradoxical anxiety
Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with FICALI.
This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures
FICALI should be discontinued in any patient who develops seizures. FICALI should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored.
FICALI should be discontinued if there is an increase in seizure frequency.

Diabetes mellitus
In patients with diabetes mellitus, treatment with FICALI may alter glycaemic control, possibly due to improvement of depressive symptoms. The doses of insulin and/or oral hypoglycaemic medications may need to be adjusted.

Suicide
As an improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for the risk of suicide.
Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk persists until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with FICALI should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.
Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.
The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing FICALI, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
If the decision is made to discontinue treatment, FICALI should be tapered (see section 4.2).

Haemorrhage
There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with FICALI. Caution is advised in patients taking FICALI, particularly in concomitant use with medicines known to affect platelet function [e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory medicines (NSAIDS), ticlopidine and dipyridamole], as well as in patients with a history of bleeding disorders.

ECT (electroconvulsive therapy)
There is limited published clinical experience of concurrent administration of FICALI and ECT, therefore caution is advisable.

Elderly patients (> 65 years of age)
A longer half-life (about 50 %) and decreased clearance values have been demonstrated in the elderly, therefore a lower initial and maximum dose should be considered.

Reduced hepatic function
FICALI should be halved to the lower end of the dose range in patients with hepatic insufficiency. When stopping FICALI therapy, gradual dose reduction should be considered.

Risk of serotonin syndrome
Co-administration with MAO inhibitors may cause serotonin syndrome. Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.
There have been reports of enhanced effects when FICALI has been given with lithium or tryptophan and therefore concomitant use of FICALI with these medicines should be undertaken with caution.

4.5 Interaction with other medicines and other forms of interaction

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 weak inhibitor of isoenzymes CYP1A2, 2C9, 2C19, 2E1 and 3A, and a weak inhibitor of 2D6.

Ritonavir:
The pharmacokinetics of single doses of FICALI were not changed by co-administration with a single dose of ritonavir (CYP3A4 inhibitor).

Ketoconazole:
Co-administration with ketoconazole (potent CYP3A4 inhibitor) has no effect on the pharmacokinetics of FICALI.

Cimetidine:
Co-administration of racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) resulted in increased plasma concentrations of the racemate (43 % increase in AUC, 39 % increase in C_{max}). Thus, caution should be exercised at the upper end of the dose range of FICALI when used concomitantly with high doses of cimetidine.

Monoamine Oxidase Inhibitors (MAOI's), Sumatriptan and Tramadol:
Co-administration with MAO inhibitors may cause serotonin syndrome.
Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.

Lithium and Tryptophan:
There have been reports of enhanced effects when FICALI has been given with lithium or tryptophan and therefore concomitant use of FICALI with these medicines should be undertaken with caution (see section 4.4).

Desipramine:
Co-administration with a single dose of desipramine (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of desipramine. Therefore, caution is advised when FICALI 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.

Metoprolol:
Co-administration with a single dose of metoprolol 100 mg (a CYP2D6 substrate) resulted in a twofold increase in the C_{max} and a 52 % increase of the AUC of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

Selegiline:
Racemic citalopram increases the AUC of selegiline by 29 %.

Other:
Pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin. However, prothrombin time was slightly increased after a single dose of 25 mg warfarin.
The International Normalised Ratio (INR) needs to be carefully monitored in patients on the combination.

Haemorrhage
Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped (see section 4.4). Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see section 4.4).

4.6 Fertility, pregnancy and lactation

The safety of FICALI in pregnant and lactating women has not been established.
Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

4.7 Effects on ability to drive and use machines

Patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. They should be warned of this possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

See secton 4.4 for suicide information.

The side-effects are listed below by body system, organ class and frequency (where applicable). Frequencies are defined as very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000) or frequency unknown.

Adverse reactions observed with FICALI are most frequent during the first one or two weeks of treatment and may decrease in intensity and frequency with continued treatment.
After prolonged administration, abrupt cessation of FICALI may produce withdrawal reactions in some patients.

Body as a whole – General disorders
Common: Nausea, insomnia, somnolence, increased sweating, diarrhoea, constipation, dizziness, fatigue, decreased appetite, sinusitis, decreased libido, pyrexia, yawning
Gender specific: Ejaculation disorder, impotence and abnormal orgasm (female)
Uncommon: Sleep disorder, taste disturbance

Cardiovascular disorders
Reported but frequency unknown: Postural hypotension

Metabolism and nutrition disorders
Reported but frequency unknown: Hyponatraemia. Inappropriate ADH secretion

Eye disorders
Reported but frequency unknown: Abnormal vision (could affect driving)

Gastrointestinal disorders
Reported but frequency unknown: Nausea, vomiting, dry mouth, diarrhoea, anorexia

General disorders
Reported but frequency unknown: Insomnia, dizziness, fatigue, drowsiness, anaphylactoid reactions

Hepato-biliary disorders
Reported but frequency unknown: Abnormal liver function tests

Musculoskeletal disorders
Reported but frequency unknown: Arthralgia, myalgia

Neurological disorders
Reported but frequency unknown: Seizures, tremor, movement disorders, 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
Reported but frequency unknown: Hallucinations, mania, confusion, agitation, anxiety, depersonalisation, panic attacks and nervousness

Renal and urinary disorders
Reported but frequency unknown: Urinary retention

Reproductive system and breast disorders
Reported but frequency unknown: Galactorrhoea, sexual dysfunction such as ejaculation disorder and anorgasmia
Frequency unknown: Postpartum haemorrhage (see section 4.4 and 4.6)

Skin disorders
Reported but frequency unknown: Rash, ecchymoses, pruritus, angioedema, sweating

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8.
Treatment:
There is no specific antidote. Treatment is supportive and symptomatic.
Gastric lavage should be carried out as soon as possible after oral ingestion.
Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants).
Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors ATC-code: N 06 AB 10. (2)

Escitalopram is a selective inhibitor of serotonin (5-HT)-uptake.
Escitalopram has minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. Escitalopram has no or very low affinity for a series of receptors including $5\text{-}HT_{1A}$, $5\text{-}HT_2$, DA D_1 and D_2 receptors, a_1-, a_2-, b-adrenoceptors, histamine H_1, muscarinic, benzodiazepine and opioid receptors.

5.2 Pharmacokinetic properties

Absorption:
Absorption is independent of food intake (mean T_{max} is 4 hours after multiple dosing).
Distribution:
The apparent volume of distribution (Vd, β/F) after administration is about 12 to 26 L/kg. The plasma protein binding of escitalopram is approximately 55 %.
Biotransformation:
Escitalopram is metabolized in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form a N-oxide metabolite. Both parent compound 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 after multiple dosing is about 30 hours and the plasma clearance after oral administration (C1oral) is about 0,6 L/min. Escitalopram and major metabolites are 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. CYP2C19 is the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6. There is linear pharmacokinetics. 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 of age):
A longer half-life (about 50 %) and decreased clearance values, due to a reduced rate of metabolism, have been demonstrated in the elderly.
Reduced hepatic function:
Escitalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of escitalopram is twice as long in patients with hepatic impairment and steady state escitalopram concentrations at a given dose will be approximately twice as high as in patients with normal liver function.
Reduced renal function:
Escitalopram is 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 < 30 mL/min).
Polymorphism:
Based on in vitro results with escitalopram, genetic polymorphism with respect to CYP2D6 is not known; with respect to CYP2C19, it may be of clinical relevance, as shown in a limited number of patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Purified talc
Silica colloidal anhydrous
Approved colourants

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25°C. Keep containers well closed.

6.5 Nature and contents of container

*Aluminium/PVC/PVDC blister strips of: 10, 14, 20, 28, 30, 49, 50, 56, 60, 90, 100, 180, 200 tablets.
* Polypropylene Securitainers with polyethylene cap: 49, 100, 200, 250, 500 tablets.
* Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special precautions required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.
106 16th Road, Building 2
Midrand
1686

8 REGISTRATION NUMBERS

FICALI 5: 41/1.2/0567
FICALI 10: 41/1.2/0568
FICALI 15: 41/1.2/0569
FICALI 20: 41/1.2/0570

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 July 2009

10 DATE OF REVISION OF THE TEXT

14 March 2021

TRINITY PHARMA

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PROFESSIONELE INLIGTING

SKEDULERINGSTATUS **S5**

1 NAAM VAN DIE MEDISYNE

FICALI 5 film-bedekte tablette
FICALI 10 film-bedekte tablette
FICALI 15 film-bedekte tablette
FICALI 20 film-bedekte tablette

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke film-bedekte tablet bevat:
Essitalopraamoksalaat gelykstaande aan 5 mg, 10 mg, 15 mg of 20 mg essitalopraam. Suikervry.
Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

3 FARMASEUTIESE VORM

Film-bedekte tablette.
FICALI 5: 'n 5,5 mm normale konvekse, wit film-bedekte tablet gebosseleer met "EC" aan die een kant en "G" aan die ander.
FICALI 10: 'n 9,5 mm x 5,5 mm langwerpige normale konvekse, wit film-bedekte tablet gebosseleer met "EC½10" aan een kant en "G" aan die ander.
FICALI 15: 'n 10,5 mm x 6 mm ellipse normale konvekse, wit film-bedekte tablet gebosseleer met "EC½15" aan die een kant en "G" aan die ander.
FICALI 20: 'n 12,5 mm x 7 mm langwerpige normale konvekse, wit film-bedekte tablet gebosseleer met "EC½20" aan die een kant en "G" aan die ander.

4 KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

Behandeling van major depressiewe episodes.

4.2 Posologie en metode van toediening

Posologie
Volwassenes:
Major Depressiewe episodes:
FICALI behoort daagliks toegedien te word as 'n enkele orale dosis van 10 mg by andersins gesonde volwassenes. Afhangende van die individuele pasiënt se respons, kan die dosis tot 'n maksimum van 20 mg per dag verhoog word.
Gewoonlik is 2 - 4 weke nodig om antidepressantrespons te verkry.
Bejaarde pasiënte (> 65 jarige ouderdom):
'n Langer halfleeftyd en verminderde opruiming is by bejaardes aangetoon, dus behoort 'n laer aanvanklike en maksimum dosis oorweeg te word.
Verswakte renale funksie:
Dosisaanpassing is nie nodig by pasiënte met ligte tot matige renale inkorting nie. Geen inligting is beskikbaar oor die behandeling van pasiënte met ernstige verswakte renale funksie (kreatinienopruiming <30 ml/min) (sien WAARSKUWINGS).
Verswakte hepatiese funksie:
Dosis moet tot die onderste punt van die dosisreikwydte gehalveer word by pasiënte met hepatiese ontoereikendheid. Wanneer FICALI terapie gestaak word, behoort geleidelike dosisvermindering oorweeg te word. FICALI word as 'n enkele daaglikse dosis toegedien.
Serotonien onttrekking:
Wanneer FICALI terapie gestaak word, behoort geleidelike dosisvermindering oorweeg te word.
Metode van toediening
Vir orale gebruik.
FICALI mag geneem word sonder om voedselinname in ag te neem.

4.3 Kontraïndikasies

- Hipersensitiwiteit vir essitalopraam of vir enige van die hulpstowwe van FICALI (sien afdeling 6.1).
- Kinders onder 18 jarige ouderdom; aangesien veiligheid en effektiwiteit nie in hierdie bevolking bevestig is nie.

Monoamienoksidaseinhibeerders:
Gevalle van ernstige reaksies is aangemeld by pasiënte wat 'n SSHI ontvang in kombinasie met 'n monoamienoksidaseinhibeerder (MAOI), en by pasiënte wat onlangs 'n SSHI gestaak het en op 'n MAOI begin is (sien afdeling 4.5). Sommige gevalle het gepresenteer met kenmerke wat ooreenstem met serotoniensindroom (sien afdeling 4.4 Klas reaksies). FICALI behoort nie in kombinasie met 'n MAOI gebruik te word nie.

FICALI mag 14 dae na staking die behandeling met 'n MAOI, begin word. Minstens 7 dae moet verloop na die staking van FICALI behandeling, alvorens 'n MAOI begin word.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Manie
FICALI behoort gestaak te word by enige pasiënt wat 'n maniese fase betree. FICALI moet met omsigtigheid gebruik word by pasiënte met 'n geskiedenis van manie/hipomanie.
Paradoksale angs
Sommige pasiënte met paniekversteuring kan verhoogde angssimptome ervaar aan die begin van die behandeling met FICALI.
Hierdie paradoksale reaksie klaar gewoonlik op binne twee weke van volgehoue behandeling. 'n Lae aanvangsdosis word aanbeveel om die waarskynlikheid van 'n paradoksale angsiogeniese effek te verminder.

Toevalle
FICALI behoort gestaak te word by enige pasiënt wat toevalle ontwikkel. FICALI behoort vermy te word by pasiënte met onstabiele epilepsie en pasiënte met gekontroleerde epilepsie moet noukeurig gemonitor word.
FICALI behoort gestaak te word indien daar 'n toename in toeval frekwensie is.

Diabetes mellitus
By pasiënte met diabetes mellitus kan behandeling met FICALI glukemiese beheer verander, moontlik as gevolg van die verbetering van depressiesimptome. Dit mag nodig wees om die dosis insulien en/of orale hipoglisemiese medikasie aan te pas.

Selfmoord
Aangesien 'n verbetering nie gedurende die eerste paar weke of meer van die behandeling mag voorkom nie, moet pasiënte noukeurig dopgehou word vir die risiko van selfmoord.
Pasiënte met major depressiewe versteuring, volwassenes sowel as kinders, kan 'n verergering van hul depressie en/of selfmoordgedagtes en -gedrag ervaar, of hulle antidepressante medisyne neem al dan nie. Hierdie risiko duur voort totdat beduidende remissie voorkom. 'n Oorsaaklike rol van antidepressante medisyne vir sulke gedrag is egter nie bepaal nie. Pasiënte wat met FICALI behandel word, moet nogtans noukeurig dopgehou word vir kliniese verergering en selfmoordneigings, veral aan die begin van 'n kursus van behandeling of op enige tydstip van dosisveranderings, hetsy dit verhoog of verlaag word.
Vanweë die moontlikheid van co-morbiditeit tussen major depressiewe versteuring en ander psigiatriese en nie-psigiatriese versteurings, behoort dieselfde voorsorgmaatreëls getref word wanneer pasiënte met 'n major depressiewe versteuring behandel word as wanneer pasiënte met ander psigiatriese en nie-psigiatriese versteurings behandel word.
Die volgende simptome is aangemeld by pasiënte wat met antidepressante behandel is vir major depressiewe versteurings asook vir ander indikasies, beide psigiatries sowel as nie-psigiatries: angs, agitasie, paniekaanvalle, slaaploosheid, geïrriteerdheid, vyandigheid (aggressiwiteit, impulsiwiteit, akatisie, hipomanie en manie). Hoewel die oorsakende verband met die ontstaan van selfmoordneigings nie bepaal is nie, moet oorweeg word om die terapeutiese regimen te verander, waaronder moontlike staking van FICALI, vir pasiënte wie se simptome erg is, skielik ontstaan óf waar dit nie deel van die pasiënt se aanvanklike simptome was nie.
Indien daar besluit word om behandeling te staak, behoort FICALI geleidelik onttrek word (sien afdeling 4.2).

Bloeding
Daar is verslae van kutane bloedingsabnormaliteite, soos ekgimose en purpura met FICALI. Sorg word aanbeveel by pasiënte wat FICALI neem, veral saam met medisyne wat bekend is om plaatjiefunksie te affekteer [bv. atipiese antipsigotika en fenotiasiene, meeste trisikliese antidepressante, aspirien en nie-steroïed anti-inflammatoriese medisyne (NSAIM's), tiklopidien en dipiridamool] asook by pasiënte met 'n geskiedenis van bloedingsversteurings.

EKB (elektrokonvulsiewe behandeling)
Daar is beperkte gepubliseerde kliniese ondervinding van gelyktydige toediening van FICALI en EKB, dus word sorg aanbeveel.

Bejaarde pasiënte (> 65 jarige ouderdom)
'n Langer halfleeftyd (ongeveer 50 %) en verlaagde opruimingswaardes is by bejaardes aangetoon, dus moet 'n laer aanvanklike en maksimum dosis oorweeg word.

Verswakte hepatiese funksie
FICALI behoort gehalveer te word tot die onderste punt van die dosisreikwydte by pasiënte met hepatiese ontoereikendheid. Wanneer FICALI-terapie gestaak word, behoort geleidelike dosisvermindering oorweeg te word.

Risiko van serotoniensindroom
Gelyktydige toediening met MAO inhibeerders mag serotoniensindroom veroorsaak. Gelyktydige toediening met ander serotonergiese medisyne (bv. tramadol, sumatriptaan) sowel as ander antidepressante met serotonergiese eienskappe kan lei tot die versterking van serotonien-geassosieerde effekte, bv. die serotoniensindroom.
Daar is verslae van versterkte effekte waar FICALI saam met litium of triptofaan gegee is en daarom moet die gebruik van FICALI met hierdie medisyne met sorg onderneem word.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

In vitro studies het getoon dat die biotransformasie van essitalopraam na sy gedemetileerde metaboliete afhang van drie parallelle weë (sitokroom P450 (CYP) 2C19, 3A4 en 2D6). Essitalopraam is 'n swak inhibeerder van isoënsieme CYP1A2, 2C9, 2C19, 2E1 en 3A, en 'n swak inhibeerder van 2D6.

Ritonavir:
Die farmakokinetika van enkele dosisse FICALI was nie verander deur gesamentlike toediening van 'n enkele dosis ritonavir (CYP3A4 inhibeerder) nie.

Ketokonasool:
Gelyktydige toediening met ketokonasool (potente CYP3A4 inhibeerder) het geen invloed op die farmakokinetika van FICALI nie.

Simetidien:
Gelyktydige toediening van rasemiese sitalopraam met simetidien (potente CYP2D6, 3A4 en 1A2 inhibeerder) het gelei tot verhoogde plasmakonsentrasies van die rasmaat (43 % toename in AOK, 39 % toename in K_{maks}). Dus behoort omsigtigheid by die bokant van die dosisreikwydte van FICALI uitgeoefen te word wanneer dit gelyktydig met hoë dosisse simetidien gebruik word.

Monoamienoksidaseinhibeerders (MAOI's), Sumatriptaan en Tramadol:
Gelyktydige toediening met MAO inhibeerders mag serotoniensindroom veroorsaak.
Gelyktydige toediening met ander serotonergiese medisyne (bv. tramadol, sumatriptaan) sowel as ander antidepressante met serotonergiese eienskappe mag lei tot die versterking van serotonien-geassosieerde effekte, bv. die serotoniensindroom.

Litium en Triptofaan:
Daar is al berig oor versterkende effekte wanneer FICALI saam met litium of triptofaan gegee word, en dus moet die gesamentlike gebruik van FICALI met hierdie medisyne met omsigtigheid onderneem word (sien afdeling 4.4).

Desipramien:
Gelyktydige toediening met 'n enkele dosering desipramien ('n CYP2D6 substraat) het gelei tot 'n tweevoudige toename in plasmavlakke van desipramien. Dus word omsigtigheid aanbeveel wanneer FICALI en desipramien gelyktydig toegedien word. 'n Soortgelyke toename in plasmavlakke van desipramien, na toediening van imipramien, was gesien toe dit saam met rasemiese sitalopraam gegee was.

Metoprolol:
Gelyktydige toediening met 'n enkele dosering metoprolol 100 mg ('n CYP2D6 substraat) het gelei tot 'n tweevoudige toename in die K_{maks} en 'n 52 % toename in die AOK van metoprolol. Die kombinasie het egter geen klinies beduidende gevolge op bloeddruk en hartklop gehad nie.

Selegilien:
Rasemiese sitalopraam verhoog die AOK van selegilien met 29 %.

Ander:
Farmakokinetiese interaksiestudies met rasemiese sitalopraam het geen klinies belangrike interaksies met karbamasepien (CYP3A4 substraat), triasolaam (CYP3A4 substraat), teofillien (CYP1A2 substraat) (enkeldosis) warfarien (CYP3A4 en CYP2C9 substraat), levomepromasien (CYP2D6 inhibeerder), litium en digoksien getoon nie. Die protrombientyd was egter effens langer na 'n enkele dosis van 25 mg warfarien.
Die Internasionale Genormaliseerde Verhouding (IGV) moet noukeurig gemonitor word by pasiënte op die kombinasie.

Bloeding
Veranderde antikoagulanteffekte mag voorkom wanneer essitalopraam gekombineer word met orale antikoagulante. Pasiënte wat orale antikoagulantterapie ontvang behoort noukeurige koagulasie monitering te ondergaan wanneer essitalopraam begin of gestaak word (sien afdeling 4.4). Gelyktydige gebruik van nie-steroïed anti-inflammatoriese medisyne (NSAIM's) mag die bloedingsneigings verhoog (sien afdeling 4.4).

4.6 Vrugbaarheid, swangerskap en laktasie

Die veiligheid van FICALI by swanger en lakterende vroue is nie vasgestel nie.
Waarnemingsdata dui op 'n verhoogde risiko (minder as 2-voudig) van postpartumbloeding na blootstelling aan SSHI/SNHI binne die maand voor geboorte (sien afdelings 4.4, 4.8).

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik

Pasiënte wat depressief is en behandeling benodig, mag ingekorte vermoë hê om te bestuur of masjinerie te hanteer. Hulle moet gewaarsku word van hierdie moontlikheid en aangeraai word om sulke take te vermy indien hul so geaffekteer word.

4.8 Newe-effekte

Sien afdeling 4.4 vir selfmoord inligting.

Die newe-effekte word hieronder volgens liggaamstelsel, orgaanklas en frekwensie (waar van toepassing) aangegee. Frekwensies word gedefinieer as baie algemeen (≥ 1/10); algemeen (≥ 1/100, 1/10); ongewoon (≥ 1/1 000, 1/100); seldsaam (≥ 1/10 000, 1/1 000); baie seldsaam (1/10 000) of frekwensie onbekend.

Newe-effekte wat by FICALI waargeneem word, kom gereeld voor gedurende die eerste week of twee van behandeling en mag afneem in intensiteit en frekwensie met voortgesette behandeling.
Na langdurige toediening kan skielike staking van FICALI onttrekkingsreaksies by sommige pasiënte veroorsaak.

Liggaam as geheel – Algemene versteurings
Algemeen: Naarheid, slaaploosheid, somnolensie, verhoogde sweet, diarree, konstipasie, duiseligheid, moegheid, verminderde eetlus, sinusitis, verlaagde libido, pireksie, gaap
Geslagspesifiek: Ejakulasieversteuring, impotensie en abnormale orgasme (vroue)
Ongewoon: Slaapversteuring, smaakversteuring

Kardiovaskulêre versteurings
Aangemeld, maar onbekende frekwensie: Posturale hipotensie

Metabolisme- en voedingsversteurings
Aangemeld, maar onbekende frekwensie: Hiponatremie. Onvanpaste ADH sekresie

Oogversteurings
Aangemeld, maar onbekende frekwensie: Abnormale visie (kan bestuur beïnvloed)

Gastroïntestinale versteurings
Aangemeld, maar onbekende frekwensie: Naarheid, braking, droë mond, diarree, anoreksie

Algemene versteurings
Aangemeld, maar onbekende frekwensie: Slaaploosheid, duiseligheid, moegheid, lomerigheid, anafilaktiese reaksies

Hepato-biliêre versteurings
Aangemeld, maar onbekende frekwensie: Abnormale lewerfunksietoetse

Muskuloskeletale versteurings
Aangemeld, maar onbekende frekwensie: Artralgie, mialgie

Neurologiese versteurings
Aangemeld, maar onbekende frekwensie: Stuiptrekkings, tremor, bewegingsversteurings, serotoniensindroom (gewoonlik gekenmerk deur 'n vinnige aanvang van veranderinge in die geestestoestand, met verwarring, manie, agitasie, hiperaktiwiteit, bewering, koors, tremor, okulêre bewegings, mioklonus, hiperrefleksie, en gebrek aan koördinasie)

Psigiatriese versteurings
Aangemeld, maar onbekende frekwensie: Hallusinasies, manie, verwarring, agitasie, angs, depersonalisering, paniekaanvalle en senuweeagtigheid

Renale en urinêre versteurings
Aangemeld, maar onbekende frekwensie: Urinêre retensie

Voortplantingsisteem- en borsversteurings
Aangemeld, maar onbekende frekwensie: Galaktorree, seksuele disfunksie soos ejakulasieversteuring en anorgasmie
Onbekende frekwensie: Postpartum bloeding (sien afdeling 4.4 en 4.6)

Velversteurings
Aangemeld, maar onbekende frekwensie: Uitslag, ekgimose, pruritus, angioedeem, sweet

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "**6.04 Adverse Drug Reactions Reporting Form**", wat aanlyn by SAHPRA se publikasies gevind kan word:
https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering

Sien afdeling 4.8.
Behandeling:
Daar is geen spesifieke teenmiddel nie. Behandeling is ondersteunend en simptomaties.
Maagspoeling moet so gou as moontlik na orale inname uitgevoer word.
Monitering van hart- en lewenstekens word aanbeveel, tesame met algemene simptomatiese ondersteunende maatreëls.

5 FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Farmakologiese klassifikasie: A 1.2 Psigoanaleptika (antidepressante)
Farmakoterapeutiese groep: antidepressante, selektiewe serotonien-heropname-inhibeerders ATK-kode: N 06 AB 10. (2)

Essitalopraam is 'n selektiewe inhibeerder van serotonien (5-HT) heropname.
Essitalopraam het 'n minimale effek op die opname van noradrenalien (NA), dopamien (DA) en gamma-aminobottersuur (GABA). Essitalopraam het geen of lae affiniteit vir 'n aantal reseptore, insluitend $5\text{-}HT_{1A}$, $5\text{-}HT_2$, DA D_1 en D_2 reseptore, a_1-, a_2-, b-adrenoseptore, histamine H_1, muskariene reseptore, bensodiasepien- en opioïedreseptore.

5.2 Farmakokinetiese eienskappe

Absorpsie:
Absorpsie is onafhanklik van voedselinname (gemiddelde T_{maks} is 4 uur na veelvuldige dosering).
Verspreiding:
Die oënskynlike volume van verspreiding (Vd, β/F) na toediening is ongeveer 12 tot 26 L/kg. Die plasmaproteïenbinding van essitalopraam is ongeveer 55 %.
Biotransformasie:
Essitalopraam word in die lewer na die demetiel- en didemetielmetaboliete gemetaboliseer. Die stikstofatoom kan ook na die N-oksiedmetaboliet geoksideer word. Die moederverbinding asook die metaboliete word gedeeltelik as glukuroniede uitgeskei.
Onveranderde essitalopraam is die prominente verbinding in plasma.
Na meervoudige dosering is die gemiddelde konsentrasies van die demetiel- en didemetielmetaboliete gewoonlik 28 – 31 % en < 5 % van die konsentrasie van essitalopraam, onderskeidelik. Biotransformasie van essitalopraam na die demetielmetaboliet word bemiddel deur 'n kombinasie van CYP2C19, CYP3A4 en CYP2D6.
Eliminasie:
Die eliminasiehalfleeftyd na meervoudige dosering is ongeveer 30 uur en die plasmaopruiming na orale toediening (C1 oraal) is ongeveer 0,6 L/min. Dit word aanvaar dat essitalopraam en die hoofmetaboliete deur beide hepatiese (metaboliese) en renale roetes uitgeskei word met die grootste deel van die dosis as metaboliete in die urien.
Hepatiese opruiming is hoofsaaklik deur die P450-ensiemstelsel. CYP2C19 is die primêre isoënsieme wat betrokke is by die demetielering van essitalopraam, gevolg deur CYP3A4 en CYP2D6. Daar is lineêre farmakokinetika. Gelykvlak plasmavlakke word bereik in ongeveer 1 week. Gemiddelde gelykvlakkonsentrasies van 50 nmol/L (gebied 20 tot 125 nmol/L) word met 'n daaglikse dosis van 10 mg bereik.
Bejaarde pasiënte (> 65 jarige ouderdom):
'n Langer halfleeftyd (ongeveer 50 %) en verminderde opruimingswaardes, as gevolg van 'n verlaagde tempo van metabolisme, is by bejaardes aangetoon.
Verswakte hepatiese funksie:
Essitalopraam word stadiger geëlimineer by pasiënte met verswakte lewerfunksie. Die halfleeftyd van essitalopraam is twee keer so lank by pasiënte met hepatiese inkorting en gelykvlak essitalopraam konsentrasie in 'n gegewe dosis, sal ongeveer twee keer so hoog wees as by pasiënte met normale lewerfunksie.
Verswakte renale funksie:
Essitalopraam word stadiger uitgeskei by pasiënte met 'n ligte tot matige verswakte renale funksie met geen groot impak op die konsentrasies van essitalopraam in die serum nie. Daar is tans geen inligting beskikbaar oor die behandeling van pasiënte met erge verswakte renale funksie (kreatinienopruiming < 30 mL/min) nie.
Polimorfisme:
Op grond van *in vitro*-resultate met essitalopraam is genetiese polimorfisme ten opsigte van CYP2D6 nie bekend nie; ten opsigte van CYP2C19 kan dit van kliniese belang wees, soos by 'n beperkte aantal pasiënte aangetoon.

6 FARMSEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

Natriumkroskarmellose
Magnesiumstearaat
Mikrokristallien sellulose
Gesuiwerde talk
Silika, kolloïed anhedriese
Goedgekeurde kleurstowwe

6.2 Onverenigbaarheid

Nie van toepassing nie.

6.3 Rakleeftyd

24 maande.

6.4 Spesiale voorsorgmaatreëls tydens berging

Stoor teen of benede 25 °C. Hou houers deeglik toe.

6.5 Aard en inhoud van die houer

*Aluminium/PVC/PVDC stulpstroke van: 10, 14, 20, 28, 30, 49, 50, 56, 60, 90, 100, 180, 200 tablette.
* Polipropileenveiligheidshouers met poliëtileendeksel: 49, 100, 200, 250, 500 tablette.
* Nie alle verpakkingsgroottes word moontlik bemark nie.

6.6 Spesiale voorsorgmaatreëls vir die wegdoen en ander hantering

Geen spesiale vereistes nodig.

7 HOUER VAN REGISTRASIESERTIFIKAAT

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8 REGISTRASIENOMMERS

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