01 | 2016

VORTIOXETINE

▼BRINTELLIX® FOR MAJOR DEPRESSION

dtbn
DRUG ASSESSMENT REPORT
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Placebo and l

Indications
Major depression in adults.

Mechanism of action and pharmacokinetics
It inhibits serotonin transporter and modulates the activation of the serotonin receptor by acting as antagonist/agonist (5-HT3 and 5-HT7 antagonist, and 5-HT1A and 5-HT1B agonist). It increases serotonin, dopamine, acetylcholine, norepinephrine and histamine.

It is taken orally and does not interact with any food. It reaches the steady state in two weeks. Plasma protein binding reaches up to 99%. It is metabolized by hepatic oxidation by CYP2D6.

Dosage and administration
The initial dose in adults <65 years is 10 mg/d (5-20 mg/d according to response). The initial dose in adults >65 years is 5 mg/d. Once the episode has been solved, treatment must be continued for at least six further months to consolidate response.

Clinical efficacy
In 10 short-term, placebo-controlled, 6-8 week, II/III phase trials, 2.5 mg/d was compared with 20 mg/d dosage. One of the studies included an active arm with venlafaxine (225 mg/d) and four with duloxetine (60 mg/d). None of these trials was designed to compare antidepressants.

The mean age was 44 years (the number of women doubled that of men) and patients included had moderate-severe depression (MADRS ≥ 22-26) and moderate anxiety. The primary endpoint was improvement of symptoms based on the lowering of scores on two scales with respect to the baseline situation, MADRS and HAMILTON. MADRS scale: range = 0-60; if <10 points, no depression. A 50% reduction is accepted as clinically relevant). Hamilton 24-item scale: range: 0-52; a score ≥18 indicates moderate-severe depression.

Global analysis revealed that vortioxetine was more effective than placebo in reducing MADRS with 5 mg/d [-2.27 points (CI95% -0.63; -3.92)], 10 mg/d [-3.57 points (-2.17; -4.97)] and 20 mg/d [-4.57 points (-2.57; -6.57)], but not with 15 mg/d. Individual studies showed no statistically significant differences between vortioxetine and placebo.

The rate of responders (secondary endpoint), defined as the percentage of patients that attained a 50% reduction in MADRS, was measured. A statistically significant difference was observed with respect to placebo (OR= 1.5-2.0) for 5, 10 and 20 mg doses. Significant differences were also found in remission rates (MADRS ≤ 10). Reduction in MADRS was greater in the active arms of the groups receiving venlafaxine and duloxetine.

Vortioxetine (10 or 20 mg/d) was compared with agomelatine (25 or 50 mg/d) in partial responders and no responders to SSRI or SSRIN. After 12 weeks, vortioxetine was more effective in reducing MADRS (-2.16 difference [CI95% -3.5 to -0.81]). However, given than neither baseline MADRS nor treatment adherence were monitored, it cannot be deduced that patients did not respond to treatment. In addition, the retrospective selection of patients and the comparator used do not support the effectiveness of vortioxetine in these patients.

Limited evidence, no benefit proven over other antidepressants and more costly

A double-blind, randomized, placebo-controlled study was performed in patients responsive to vortioxetine at 12 weeks of treatment. Treatment was extended for 24 further weeks and the risk of relapse was observed to be higher for placebo than for vortioxetine (5 or 10 mg).

Safety
Adverse Reactions
Common: nausea (31%), migraine, dizziness, diarrhea, vomiting and constipation. **Other (≥ 2%):** abnormal dreams, loss of appetite, generalized pruritus and flu. After one year of treatment, patients reported nausea (17.5%), migraine (13.2%) and nasopharyngitis (10.5%). Regarding the characteristic risks of antidepressants:

· Sleep disorders were similar to placebo.

· Episodes of sexual dysfunction were reported by 38%, 48% and 32% of patients receiving vortioxetine, duloxetine and placebo, respectively. The incidence of sexual dysfunction in vortioxetine at 15 mg (43%) and 20 mg (46%) was similar to that in duloxetine.

· No increase in the incidence of akathisia or dyskinesia vs placebo was observed.

ABSTRACT

No comparative studies have been performed versus the antidepressants of choice.

There is no evidence that it has similar or higher effectiveness than other antidepressants.

Indirect studies suggest that vortioxetine is less effective than duloxetine and venlafaxine.

The safety profile -except for nausea- is similar to that of SSRIs and SNRIs, although long-term studies have not been performed.

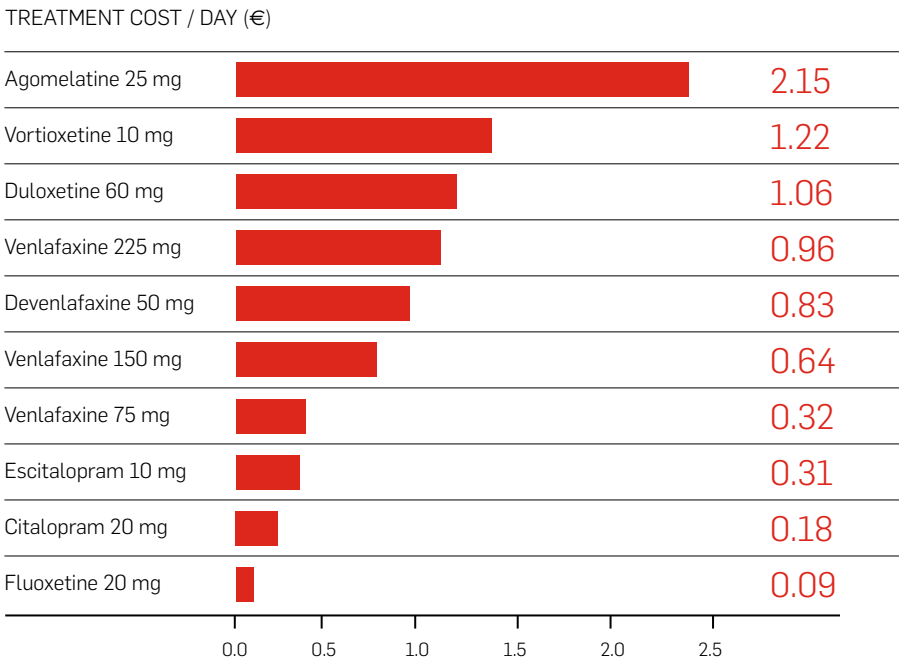
Not all studies have proven that it is more effective than placebo.

There is more evidence on the effectiveness of SSRI antidepressants, and they have a better risk/benefit balance. Therefore, SSRIs should be the treatment of choice.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



Contraindications

Hypersensitivity to the active ingredient and excipients included.
Concomitant use with MAO-A inhibitors.

Warnings and precautions

The treatment must be discontinued in case of suicidal thoughts, signs or symptoms of malignant serotonin or neuroleptic syndrome, seizures or unstable epilepsy and manic phases.
Caution in patients:
· with bleeding disorders or on anticoagulant or antiplatelet treatment
· at risk of hyponatremia (elderly patients with liver cirrhosis or simultaneously treated with drugs that cause hyponatremia) and consider treatment discontinuation in case of symptomatic hyponatremia.
Vortioxetine did not cause a clinically significant increase in the QT interval, although it tended to increase with 40 mg/d.
Special caution should be taken, especially at the start of treatment or dose change.

Usage in special situations

Paediatrics: not recommended. **Patients older than 65 years:** start with 5 mg. Caution should be taken at doses >10 mg/d. **Mild to moderate renal or liver impairment:** adjustment is not necessary. If severe, caution. **Pregnancy:** limited data (do not use). **Breastfeeding:** risk for infants is not excluded.

Interactions

Its use in combination with irreversible, non-selective MAO inhibitors is contraindicated.

Monitoring should be intensified if the patient needs combined treatment with other drugs:
· Reversible, selective MAO-A inhibitor (moclobemide) and reversible, non-selective MAO inhibitors (linezolid).
· Irreversible, selective MAO-B inhibitors (selegiline, rasagiline)

The administration of serotoninergic drugs (tramadol, antidepressant triptans, neuroleptics, mefloquine and bupropion) may cause serotoninergic syndrome and reduce seizure threshold. Due to the lack of experience with concomitant electroconvulsive therapy, it should be administered with caution.

Do not use at doses >10 mg/d along with drugs that are metabolized through CYP2D6 or with a potent inhibitor of this cytochrome. When administered in combination with the drugs metabolized through the cytochrome P450, the dose of vortioxetine should be adjusted according to patient's response. The use of alcohol is not recommended during treatment with antidepressants.

Due to the potential increased risk of bleeding, combined treatment of oral anticoagulants or antiplatelet agents and serotoninergic drugs should be administered with caution.

The effects of serotoninergic drugs have been reported to be intensified when administered in combination with lithium or tryptophan.

EMA's Risk Management Plan[11]

Drug dependence.
Safety and tolerance in patients ≥ 65 at a dose of 15 and 20 mg/d.
The quality of the analysis of adverse event reports should be improved.

Place in therapeutics

Selective serotonin reuptake inhibitors (SSRIs) are the antidepressants on which more evidence is available and with a better risk/benefit balance. Therefore, SSRIs should be the treatment of choice. In moderate-severe major depression, it is recommended to start treatment with a SSRI or a NSSRI.[1,6,12-13]

Vortioxetine has only been proven to be effective for the treatment of depression when compared with placebo, although it was not found to be superior in all studies. No comparative studies of vortioxetine vs other antidepressants have been carried out. However, a meta-analysis that included active treatments suggested that the improvement of symptoms was milder with vortioxetine as compared to venlafaxine and duloxetine in indirect comparisons.[17]

In addition, in non-responders to other treatments, vortioxetine showed to be superior to agomelatine, although this finding should be taken with caution due to the retrospective selection of patients and the comparator selected.

The Company tried to associate its use with an improvement in cognitive impairment in patients with depression, but the results do not provide evidence that it has an effect beyond the antidepressant action.

The fact that vortioxetine has a different mechanism of action does not mean that it provides more clinical benefit. Its safety profile looks similar to that of SSRI and NSSRI, although head-to-head studies have not been performed yet. There is no need for tapering off to stop treatment. Postmarketing monitoring is required to document rare severe adverse events.

Presentation

Brintellix® (Lundbeck) 5 mg 28 tablets (17.05 €), 10 mg 28 tablets (34.09 €), 20 mg 28 tablets (54.54 €)

References

Based on the Therapeutic Positioning Report.

Servicio Navarro de Salud
Osasunbidea

INTERNATIONAL SOCIETY OF DRUG BULLETINS

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