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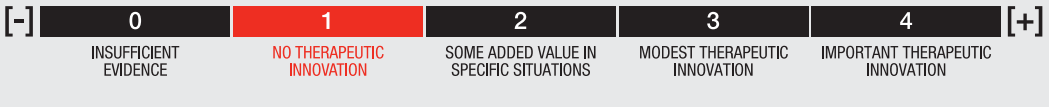
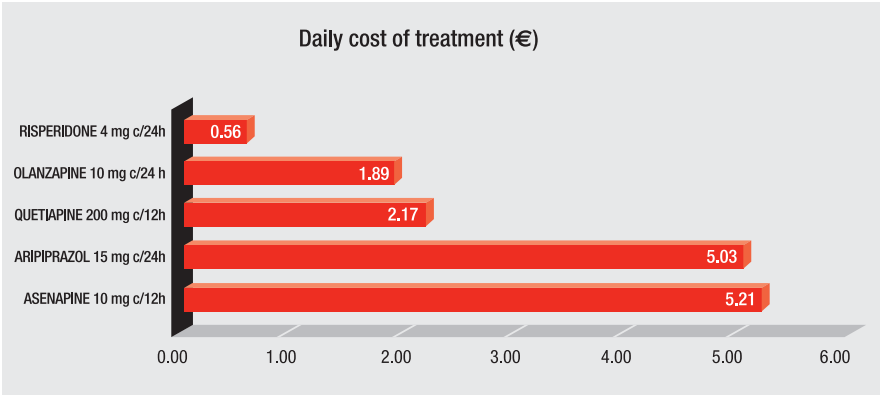
Asenapine (▲Sycrest®) for maniac episodes

Another drug with no advantages and complicated to administer





- Asenapine is an antipsychotic drug is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.
- Statistically significant improvements have been observed in comparison to placebo in the YMRS scale score, although the benefits are of scarce magnitude and uncertain clinical relevance.
- The drugs safety profile is similar to other atypical antipsychotics. The most characteristic adverse effects include hypersensitivity reactions and oral hypoesthesia.
- The drug is made exclusively for sublingual use as it is ineffective if ingested. It should be taken 10 minutes before any food or water is taken and 10 minutes after any other drug. Its particular route of administration is an important inconvenience.

It is preferable to use risperidone or olanzapine *

Therapeutic indications[1]

Treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. There is no approved indication in schizophrenia.

Mechanism of action and pharmacokinetics[1]

The mechanism of action is not fully known. The efficacy is considered to be due to antagonistic activity of the D2 and 5-HT2A receptors.

It is rapidly absorbed after sublingual administration. The T max is 0.5-1.5h, and the bioavailability is 35%. It is not absorbed through the oral route. It is eliminated through both the liver and kidneys and the half life is 24h.

Posology and method of administration[1]

Monotherapy: start with 10 mg/12h. It can be reduced to 5 mg/12h depending on the clinical evaluation. In combination therapy: start with 5 mg/12h. The dose can be increased up to 10 mg/12h.

Route of administration: sublingual. The tablet should not be extracted from he blister until it is to be taken, and should always be manipulated with dry hands. No pressure should be applied against the blister, nor should it be cut or broken. The tablet should be taken 10 minutes before any food or beverage intake and 10 minutes after intake of any other medication.

Clinical efficacy

The efficacy in manic episodes has been evaluated in various trials with a maximum duration of 12 weeks. It has not been evaluated in bipolar depression and comparative data with other antipsychotics are limited. The primary endpoint is the score on

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.

the Young Mania Rating Scale (YMRS), a scale of 11 items elaborated to measure the intensity of manic symtoms during the last 48h. This score is based on the subjective data from the patient and additional data from an observer. The score ranges from 0 to 60, and Mania is defined by a YMRS total score greater than or equal to 12.

In two trials[3,4] of 3-week duration , asenapine showed a statistically significant reduction in the YMRS score vs placebo, but lower efficacy compared to olanzapine. In the first trial, the difference in scores with respect to the baseline was -11.5±0.8 with asenapine, 7.8±1.1 with placebo (p=0.007) and -14.6±0.8 with olanzapine (p<0,0001 compared to placebo).

In the second trial, the results on the same comparisons were as follows: asenapine, -10.8±0.8; placebo, -5.5±1.0 (p<0.0001) and olanzapine, -12.6±0.8 (p<0.0001 compared to placebo). Both studies presented a high rate of withdrawals (33%).

During the 9-week extension trial[5] the average change in YMRS score was between -27.3 and -23.7 with asenapine and olanzapine. Asenapine did not show non-inferiority with respect to olanzapine.[2]

Among the limitations of this study, no reason is given to justify the chosen non-inferiority margin of 4 points as clinically relevant, and the statistical power calculation was not correct.

In the trial on add-on therapy with lithium or valproate[6], the change in YMRS after 3 weeks was -10.3±0.8 and -7.9±0.8 with asenapine and placebo respectively. The clinical relevance of this difference is questionable, especially in the absence of an active comparator. The EMA concluded that the global analysis supports the use of asenapine as an additional option in combination with mood stabilizing treatments.[2]

In one meta-analysis[8] its efficacy was superior to placebo but inferior to olanzapine in the score on manic evaluation scales, and in withdrawals from treatment after 3 weeks (surrogate endpoint). Another meta-analysis[9] with the same primary endpoint concluded that the majority of the drugs presented scarcely higher efficacy compared to placebo, with no clear superiority of one drug to another.

Safety

Adverse reactions[1]

Very frequent (>10%): somnolence and anxiety. **Frequent (1-10%):** weight gain and increased appetite, extrapiramidal effects (dystonia, acathisia, dyskinesia, parkinsonism), sedation, dizzyness, dysgeusia, oral hypoesthesia, elevated alanin transferase levels, muscular rigidity and fatigue. **Less frequent (<1%):** hyperglycemia, syncope, sexual dysfunction, heart disorders, hypersensitivity with angiooedema, hypotension, oedema, neonatal abstinence syndrome.10

Contraindications

Hypersensitivity to the main active or any of the excipients.

Precautions[1]

Patients should be forewarned of a tingling or swelling sensation of the tongue and mouth which could last up to one hour.

This drug should not be admnistered to elderly patients with dementia related psychosis, severe liver failure, malign neuroleptic syndrome or late dyskinesia. It can be used with caution in individuals with previous history of seizures, or diseases that can cause seizures. It can induce orthostatic hypotension, dysphagia and hyperprolactinemia. It can also provoke a malign neuroleptic syndrome in patients with Parkinson's disease or dementia with Lewy bodies. Precaution should be taken in patients with cardiovascular disease or family history of prolonged QT interval, and the concomittant use of drugs that could prolong the QT interval. Given the risk of hyperglycemia, diabetes patients or those with relevant risk factors should be closely monitored.

Interactions[1]

Precaution should be taken when combined with other drugs that act at the central nervous system. Alcohol should be avoided during treatment.

Fluvoxamine can increase plasma levels of asenapine. The use of asenapine can increase the effects of certain antihypertensives due to alpha-1 antagonism, with the possibility of provoking orthostatic hypotension. The effects of levodopa and dopaminergic agonists can also suffer antagonism from asenapine. Should the combination be necessary then the minimum efective dose should be given.

Asenapine is a weak inhibitor of CYP2D6, and thus should be administered with precaution if combined with drugs that are substrates and inhibitors of CYP2D6: paroxetine, imipramine, destrometorfan.

Use in special groups[1]

Children and adolescents: do not employ as there are no data available. **Elderly:** precaution. **Renal failure:** no dose adjustments are necessary. There is no experience in severe renal failure (Cr Cl <15 mL/min). **Liver failure:** if mild, no dose adjustments are necessary; moderate (Child-Pugh class B), precaution; severe, (Child-Pugh class C), not recommended. **Pregnancy:** use only if the potencial benefit outweighs the risks. **Breastfeeding:** not recommended.

Place in therapeutics

Bipolar disorder is characterized by oscillations in mood with manic phases, hypomanic and mixed phases (excitement, euphoria, and grandiosity) that generally alternate with episodes of depression (sadness, inhibition and suicidal ideation). Clinically different forms can be distinguished. The Type I Bipolar disorder includes the appearance of mania or a mixed episode, and depressive states. In Type II bipolar disorder the patient experiences less severe manic episodes, denominated hypomanic phases, and depressive states.[12]

Management is supported by psychosocial interventions and psychopharmacology in acute phases –manic and depression– and prophylaxis with mood stabilizers. The drugs used include: mood stabilizers (lithium and anticonvulsants), antipsychotics (first and second generation) and antidepressants which are employed in monotherapy (mild and moderate cases) or combined (moderate to severe cases).[12]

In the management of acute manic episodes, the use of risperidone, olanzapine, quetiapine, aripiprazol and lithium are recommended[12], while haloperidol, ziprasidone and asenapine are alternatives. In a recent meta-analysis[8], antipsychotics proved more effective than mood stabilizers (lithium, anticonvulsants) and placebo in manic episodes. Haloperidol was the most effective antipsychotic, while olanzapine and risperidone showed a better efficacy-tolerance relationship[8]. The efficacy of asenapine has not been adequately evaluated after 12 weeks of treatment in acute mania, and in cases of mixed episodes or type I bipolar disorder. Other antipsychotics such as olanzapine, quetiapine or risperidone depot have shown efficacy on relapse prevention in mania or depression after one year of treatment[11].

Presentations

Sycrest® (Lundbeck), 5 y 10 mg 60 tablets (156.32 €)

References

A complete report on Asenapine can be found at: http://www.dtb.navarra.es

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