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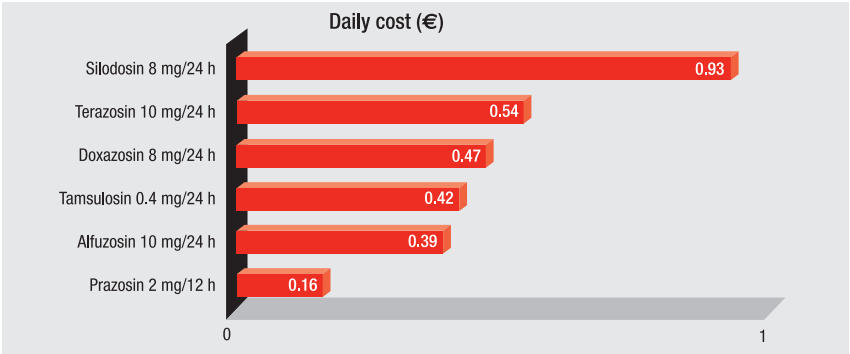
Silodosin▲ (Urorec®, Silodyx®) for benign prostatic hyperplasia

Similar efficacy but more ejaculation disorders



- Silodosin is another alpha blocker indicated for symptomatic management of benign prostatic hyperplasia.
- Its efficacy is similar to other drugs within the same pharmaceutical class, showing equivalence with tamsulosin.
- There is a high incidence of retrograde ejaculation and anejaculation associated with its use.
- Its cost is higher than the alternatives with no additional advantage over tamsulosin.

Therapeutic indications[1]

Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)

Mechanism of action and pharmacokinetics[1]

Silodosin is an antagonist of alpha-adrenergic receptors, with a high affinity for α_{1A} adrenergic receptors mainly found in the urinary tract. It produces relaxation of the smooth muscle in these tissues, thus decreasing bladder outlet resistance.

The drug presents a rapid absorption which is proportional to the dose. Distribution occurs through binding to plasmatic proteins in 96.6%. It is metabolized via the glucuronidation pathway, alcohol dehydrogenase and aldehyde dehydrogenase and oxidation, mainly through CYP3A4. Silodosin glucuronide is an active metabolite that reaches plasmatic concentrations four times that of silodosin. Elimination occurs mainly through urine and faeces. The elimination half-life of the drug and its glucuronide are 11 and 18 hours respectively.

There are other alpha blockers available with less adverse effects and at a lower cost

Posology and method of administration[1]

One 8 mg capsule daily, via oral route. In cases of moderate renal impairment treatment starts with 4 mg daily, and depending on the patient's response, the dose can be increased to 8 mg daily after a week.

Clinical efficacy

The assessment report issued by the EMA[2] mentions three phase III, randomized, double-blind clinical trials. They included patients diagnosed with symptoms affecting the lower urinary tract associated with BPH and an IPSS (International Prostate Symptom Score) score ≥ 13. The duration of the studies was 12 weeks of treatment with the comparators. This was preceded by a 4-week period of treatment with placebo in order to select patients with no response to placebo. In this previous phase, 29% of the patients were excluded on obtaining a favou-

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.

rable response to placebo, which is an important aspect to bear in mind when extrapolating the results to clinical practice.

The primary endpoint under evaluation was the change from baseline in the total IPSS score at week 12 of the study or in the last observation carried forward. In all trials silodosin showed statistical superiority compared to placebo.

The IPSS consists of 7 questions to evaluate urinary symptoms in the last month: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. The questions score from 1 to 5 according to the frequency of symptoms. The maximum score is 35 points. Symptoms of BPH are classified as mild (0-7 points); moderate (8-19) or severe (20-35). There are sub-scales with respect to irritable and obstructive symptoms.

The IT-CL-0215 trial which has not been published, included a group treated with 0.4 mg daily tamsulosin. The comparison of silodosin with tamsulosin did not show statistically significant differences. Criteria of non-inferiority are complied with for which a margin of 1.5 points was established. The results are described in the table.

The minimum difference in the IPSS of clinical relevance was considered 2 points.

Treatment group	No of patients	IPSS Basal value mean±SD	Change with respect to basal value	Difference (95%CI) between silosodin and comparator
Silodosin 8mg/24 h	371	19±4	-7.0	
Tamsulosin 0.4 mg/24 h	376	19±4	-6.7	-0.3 (-1.0 a 0.4)
Placebo	185	19±4	-4.7	-2.3 (-3.2 a -1.4)

Safety[1,2]

In the clinical studies, 1,581 patients had received 8 mg silodosin daily. Of these, 961 patients (62.4%) were treated for at least 6 months and 384 patients (24.9%) were under therapy for 1 year. The product was on the Japanese market since January 2006.

The adverse reactions notified during the clinical trials for which there is a reasonable cause and effect relationship are:
Very common (≥ 10%): retrograde ejaculation, anejactulation.
Common (1-10%): dizziness, orthostatic hypotension, nasal congestion, diarrhoea.
Uncommon (0,1-1%): reduction in libido, erection disorders, nausea, dry mouth.
Unknown frequency: syncope, intraoperative floppy iris syndrome

Risks

Intraoperative floppy iris syndrome. This syndrome has been described in some patients previously treated or under treatment with alpha blockers during cataract surgery. This agent is not recommended in patients pending cataract surgery. Patients already taking alpha blockers are recommended to discontinue their treatment before surgery, although the benefits and precise duration of this suspension has not been established.

Orthostatic hypotension, syncope. At the onset of the first symptoms (eg: postural dizziness), the patient should sit down or lie down until the symptoms disappear. This agent is not recommended to patients that suffer from orthostatic hypotension.

Failure in diagnosing prostate cancer. Before initiating and during treatment with silodosin, digital rectal examination and determinations of specific prostate antigen should be performed to rule out prostate cancer.

Ejaculation disorder. Retrograde ejaculation is the most frequently notified adverse reaction (23.6%) in clinical trials and during long-term use. It could temporarily affect masculine fertility. It is reversible after a few days of interrupting treatment.

In the IT-CL-0215 trial, 14% of the patients treated with silodosin communicated the incidence of retrograde ejaculation when compared to 2% among those under tamsulosin. It did not suppose a major problem for the majority of the patients although it was the main cause for withdrawals from the study (3.9%).

Interactions:

Concomittant use with other alpha adrenergic blockers is not recommended.

Potent inhibitors of the CYP3A4 (ketoconazole, itraconazole, ritonavir): concomitant use with this agents is not recommended.

PDE-5 inhibitors (sildenafil, tadalafil, vardenafil): in patients over 65 years of age, positive orthostatic tests were slightly more frequent while under treatment with silodosin. Monitor for possible adverse reactions.

Antihypertensive agents: in the programme of the clinical trials no increase in the incidence of orthostatic hypotension was observed in patients treated with antihypertensive agents. However, precaution should be taken when initiating concomitant treatment and physicians should be vigilant with these patients.

Special situations

Renal impairment: in moderate renal failure (Clcr = 30-50 mL/min), start with 4 mg daily. Silodosin is not recommended in severe renal failure (ClCr <30 mL/min).

Hepatic impairment: no adjustment in posology is necessary in mild and moderate hepatic impairment. Given that no data are available, its use is not recommended in severe hepatic impairment.

Place in therapeutics

Management of BPH consists in watchful waiting while symptoms are still moderate. When symptoms become more important, alpha blockers produce some symptomatic relief. The co-morbidity of the patient should be taken into account when choosing an active substance within the class of these agents, given that doxazosin, terazonsin and prazosin produce reductions in blood pressure. The 5 α-reductase inhibitors (finasteride and dutasteride) are less effective in reducing symptoms than alpha blockers. The evidence on phytotherapy is scarce. When pharmacological management is not sufficient to control symptoms, then other alternatives may be required including thermotherapy or surgery[5,6].

Silodosin is another drug incorporated in the class of alpha blockers. It presents high affinity towards the urinary system, and while not having shown differences compared to other agents within the same class, a higher incidence of adverse effects have been observed.

Presentacions

UROREC® (Recordati), SILODYX® (Almirall) 4 mg 30 capsules (13.92 €), 8 mg 30 capsules (27.85 €). Prescription Medicine only.

References

A full report on silodosin is available at: http://www.dtb.navarra.es

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