NALOXEGOL

▼MOVENTIG® FOR OPIOID-INDUCED CONSTIPATION

dtbn
DRUG ASSESSMENT REPORT
www.dtb.navarra.es
DTB_Navarre

No data available on the target population

Indications
Treatment of opioid-induced constipation in adult patients who have an inadequate response to laxatives.
It is only reimbursed for oncologic patients and requires inspection visa.

Mechanism of action
Pegylated derivative of the μ-opioid-receptor antagonist. It attaches to the μ-opioid-receptors of the gastrointestinal tract.

Administration
Oral: The recommended dose is 25/day. It must be taken on an empty stomach at least 30 minutes before the first meal of the day or 2 hours after the first meal. When treatment is started, all currently used laxatives should be stopped until its clinical effect is determined.

Comparators
Methylnaltrexone has the same mechanism of action as naloxegol but it is administered by subcutaneous injection. Its efficacy and safety profile have only been tested in patients in palliative care.

Efficacy
Its efficacy has been studied in two 12-week pivotal phase III trials (Kodiac 4 and 5) in 1325 patients with non-cancer pain who had taken a dose of naloxegol of 12.5 mg and 25 mg for at least 4 weeks and had a confirmed diagnosis of opioid-induced constipation. The use of rescue laxatives was allowed (bisacodyl and enema).
A total of 54% of study patients reported to have an inappropriate response to laxatives defined as the simultaneous occurrence of moderate to severe symptoms of opioid-induced constipation while taking laxatives for a minimum period of 4 days in the two weeks prior to the study.
The primary endpoint was response to treatment, defined as 3 or more complete spontaneous bowel movements (CSBMs) per week and the increase by one or more CSBMs per week as compared to the baseline situation in, at least, 9 of the 12 weeks on treatment, and in 3 of the 4 last weeks. A 10% increase in the number of responders was considered a clinically relevant improvement.

A statistically significant improvement was observed with the 25 mg dose in the primary endpoint in patients with an inappropriate response to laxatives. No statistically significant differences were observed in the subgroup of patients without inappropriate response to laxatives.

No comparative studies are available vs. other laxatives alone or in monotherapy

The use of rescue laxatives (bisacodyl) at least once was: in the Kodiac 4 study: 72%, 63.4% and 54.7% for placebo, 12.5 and 25 mg respectively. In the Kodiac 5 study: 70.7% 57.3% and 57.3% for placebo, 12.5 and 25 mg respectively.
No data are available on the efficacy of the drug in patients with opioid-induced constipation and cancer pain due to the small sample (n=14).

Safety
Safety was assessed in four phase III trials, one of which had a duration of 52 weeks (open trial). The placebo-controlled trials had a duration of 12 weeks. The manufacturer is required to perform two post-marketing studies to determine the cardiovascular safety profile of the drug and its safety in oncologic patients.

Adverse reactions
The most frequent adverse events occured in patients who received the 25-mg dose, and these included gastrointestinal disorders (abdominal pain, diarrhea, nausea, vomits, flatulence) and headache. The most common severe adverse event was pneumonia (<1%).
The patients in the 25-mg naloxegol group were more likely to discontinue their treatment due to adverse events as compared to the 12.5-mg group (10.3% vs. 4.8%, respectively).

ABSTRACT

The most common adverse reaction include dose-related gastrointestinal disorders. Although its safety profile is considered acceptable and no warning signs have been observed in terms of cardiovascular safety, a slight increase of blood pressure and syncope has been observed.

Observational post-marketing studies should be performed to determine its potential cardiovascular risk, and safety profile in patients with cancer.

Its efficacy has only been proven in patients with constipation caused by opioids for non-cancer pain. No data are available on patients with cancer-related pain.

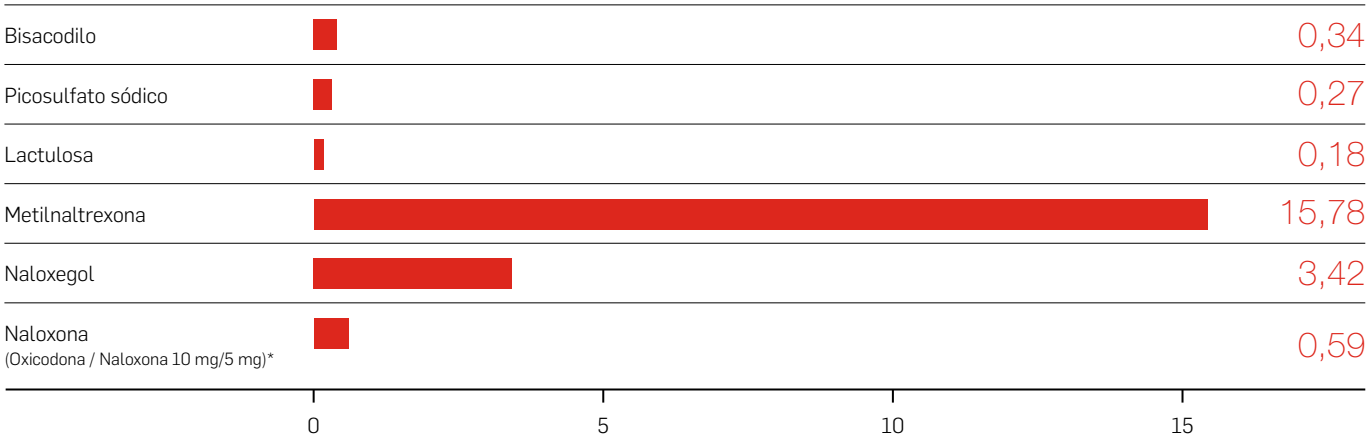
The cost per patient is higher compared to other rescue laxatives.

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.

TREATMENT COST / DAY (€). Bot Plus 2.0, June 2017



(*) Cost of naloxone: calculated by substracting the cost of oxycodone to the associated marketed drug.

Although no alarm signs have been observed in terms of cardiovascular safety, a slight increase of blood pressure and syncope has been found.
Naloxegol did not interfere with analgesia, and no clear signs of opioid withdrawal syndrome were observed during treatment.

Contraindications

Gut obstruction (or patients at high risk of gut obstruction)
Cancer with high risk of gastrointestinal perforation (underlying neoplasm of the gastrointestinal tract or the peritoneum; recurrent, advanced ovarian cancer, or ovarian cancer treated with an inhibitor of the vascular endothelial growth factor (VEGF).
Concomitant use of potent CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole, protease inhibitors, etc.)

Warnings and precautions

Not recommended in patients with severe liver failure.
Although naloxegol hardly penetrates the blood-brain barrier the development of the opioid withdrawal syndrome can occur.

Use in special situations

Mild renal impairment: Dose adjustment is not required. **Moderate to severe renal impairment and patients on treatment with moderately potent CYP3A4 inhibitors (diltiazem or verapamil):** the recommended starting dose is 12.5 mg/day, which can be increased to 25mg/day if the patient shows good tolerance to the starting dose.

Place in therapeutics

Opioid-induced constipation is treated with non-pharmacological therapies and laxatives. The recommended starting therapy includes the use of stimulant or osmotic laxatives, which can be combined when appropriate. When response is inadequate, an emollient laxative (paraffin) is added, and suppositories or enemas are introduced as rescue therapies. Methylnaltrexone is reserved for patients treated with opioids unresponsive to other laxatives.
Naloxegol has been tested in monotherapy for constipation caused by opioids in patients with non-cancer pain and patients unresponsive to laxatives. Pivotal trials have consistently shown the effectiveness of the 25-mg dose vs placebo in patients with an inadequate response to laxatives, but inconsistent results have been obtained with the 12.5mg dose. No statistically significant differences were observed in patients without inappropriate response to laxatives. Therefore, the authorization is restricted to patients with an inadequate response to laxatives.
No direct comparative studies have been performed of naloxegol vs other laxatives in monotherapy or in combination, which is normal practice. Only indirect comparisons have been conducted by the NICE where patients with an inadequate response to laxatives in the Kodiac trials 4 and 5 treated with naloxegol were compared with general populations of the trials performed with methylnaltrexone and naloxone / oxycodone. In conclusion, there is no sufficient evidence demonstrating that any difference exists between naloxegol and methylnaltrexone or naloxone / oxycodone.
Its efficacy has only been proven in patients with constipation caused by opioids for non-cancer pain. There is no scientific basis supporting that the pharmacodynamics of naloxegol is different in patients with cancer pain. However, no data are available on patients with cancer pain, and naloxegol should be prescribed with caution in this population.
Naloxegol can only be considered an option in patients with opioid-induced constipation who have an inadequate response to regular laxative therapy, including hygienic-dietary measures.

Presentations

Moventig® 30 film-coated tablets, 12.5 mg (102.56€), 25 mg (102.56€)

References

Evaluation report. https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-naloxegol-Moventig-estrenimiento.pdf