Pharmacotherapeutic report, summary

Nalmefene (Selincro®) in cases of alcohol dependence

Recommendation made by CVZ on 7-8-2013, based on an Evaluation of the WAR (Scientific Advisory Committee)

The WAR has drawn up a pharmacotherapeutic report for the medicine nalmefene (Selincro®) in a film-coated tablet with 18.06 mg active ingredient. Its therapeutic value was determined via comparison with naltrexon. They reached the following conclusions.
- For the treatment of alcohol dependence, the therapeutic value of nalmefene is equal to that of naltrexon.

Medicine. Nalmefene (Selincro®), film-coated 18.06 mg tablet for oral use

Registered indication. 'Selincro® is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (*Drinking Risk Level (DRL)),* without physical withdrawal symptoms and who do not require immediate detoxification. Selincro® should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Selincro® should be initiated only in patients who continued to have a high DRL two weeks after initial assessment.'
Posology. 1 tablet 1x/day, orally, as-needed. This means on each day the patient perceives a risk of drinking alcohol, one tablet should be taken, preferably 1-2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, he/she should take one tablet as soon as possible. The maximum dose of nalmefene is one tablet per day.

Mechanism of action. Nalmefene is a modulator of the brain's opioid system, with a distinct μ, δ and κ receptor profile. *In vitro* studies have demonstrated that nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and a partial agonist activity at the κ receptor. Alcohol intake stimulates the release of β endorphin (ligand for the β opioid receptor), enkephalin (ligand for the δ opioid receptor) and dynorphin (ligand for the κ opioid receptor). The release of these substances, the body's own substances, arouses a pleasurable and euphoric sensation. The selective antagonists of the μ and δ opioid receptors of naltrexon – which has been in use for longer – are known to inhibit the release of these substances. The clinical effect is to reduce alcohol consumption, possibly by modulating cortico-mesolimbic functions. A Positron Emission Tomography (PET) study of health volunteers revealed a very high and rapid occupancy (94% to 100% within 3 hours after intake) of the brain's μ opioid receptor after a single and repeated daily dose of 1 tablet nalmefene per day. The high occupancy (83% to 100%) persisted up to 26 hours after administration. This explains the possibility of taking nalmefene on an 'as-needed' basis.

Summary of the therapeutic value

Intended effects. Based on the results on the primary endpoints 'reduction in heavy drinking days (HDD) and total alcohol consumption', it is apparent that nalmefene statistically significantly reduces the alcohol consumption of patients with alcohol dependence. In comparison with placebo, nalmefene has an additional treatment effect that is translated into a reduction of about two HDDs per four weeks and a 10-gram reduction (1 standard glass) in total alcohol consumption per day. Based on an indirect comparison with naltrexon, there is no indication of a proven clinically relevant difference in intended effects of nalmefene and naltrexon. Both medicines have the same mechanism of action. In view of the fact that the effect of both nalmefene and naltrexon is modest, the chance of demonstrating a clinically relevant difference between the two medicines is small. In conclusion, the favourable effects of nalmefene are similar to those of naltrexon for the treatment of alcohol dependence over a period of three to six months.

Unintended effects. The use of nalmefene leads to discontinued treatment as a result of side effects in 10% of cases. The most frequent side effects were nausea, dizziness, insomnia and headache. Most of these responses occurred at the start of treatment and were transitory. There are few differences in the side effects of nalmefene and oral naltrexon. Data are lacking on the safety of using nalmefene in the long term.

Experience. The EMA recently registered nalmefene for the treatment of alcohol dependence. As a result experience is still extremely limited. Naltrexon was marketed in the USA in 1994 for the treatment of alcohol dependence and has been marketed in the Netherlands since 2004; ample experience has been gained with this medicine.

Applicability. There are no major differences in applicability between nalmefene and naltrexon, though the former can be put to a slightly broader use.
Ease of use. There are no major differences between nalmefene and naltrexon.

Final conclusion.
The use of nalmefene for the treatment of alcohol dependence during three to six months in combination with psychosocial support leads to a modest but clinically relevant reduction in alcohol consumption. Both the degree of reduction in alcohol intake and the nature and severity of the side effects that result from treatment with nalmefene are comparable with treatment using naltrexon. This conclusion is based on an indirect comparison between the results of placebo-controlled research with nalmefene and the results of a Cochrane review on naltrexon. The therapeutic value of nalmefene is comparable with naltrexon for the medicinal treatment of alcohol dependence that focuses on reducing alcohol consumption.

*The original text of this excerpt from a **WAR-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's WAR-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.