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DEVELOPING • MANUFACTURING • SUPPLYING

Naltrexone Implants

Manufactured by NalPharm Ltd

Background to Nalpharm

NalPharm is a specialist pharmaceutical company supplying proprietary branded medications and generic drugs in the area of addictions medicine. It also develops innovative formulations and manufactures unlicensed medicines exclusively for the treatment of chemical addictions with the specific aim to improving the lives of patients.

Approximately 230 million people worldwide used illicit drugs in 2010 (5% of the world population). The United Nations Office for Drugs and Crime has estimated that the global cost of drug addiction treatment to be $250 billion per year if all addicts were treated.

NalPharm is positioning itself as a leading worldwide developer, manufacturer and supplier of medicines used in the treatment of addictions to meet a growing global demand.

Introduction

There are 12-21 million heroin users worldwide. This figure has been stable for some years but the social, health and economic impact continues to rise. Over the past 50 years, the main focus of opiate addictions medical treatment has been in harmminimization strategies using opiate substitutes. In the past two decades the more widespread use of intramuscular naltrexone depots and implants is transforming the opiate treatment landscape.

What is Naltrexone?

Naltrexone is an opiate antagonist that inhibits the μ-opioid receptor in the brain. It blocks the effects of all opiates including heroin, methadone, morphine, codeine and oxycodone, and reducing the ‘pleasure‘ or ‘highs’ associated with alcohol consumption. It can therefore help patients to remain abstinent in opiate and alcohol dependence.

Naltrexone enters the brain and nervous system and attaches itself to small areas called receptor sites. For heroin to produce its effects, it must get to these same receptor sites, but naltrexone stops heroin getting to them for up to three days after an oral dose. These receptors are part of the complex reward mechanisms that motivate us and lead to repetitive behavior. If the reward is blocked, the craving and dependence behavior reduces and new behaviors reassert themselves with time. It works well for opiate addiction and often but less predictably in alcohol dependence.

Naltrexone was synthesized in the 1960s and first used clinically in the early 1970s. It soon became evident that its therapeutic potential was undermined by poor compliance with oral preparations. The first animal studies using depot preparations started in the mid 1970s and by the early 1980s, human studies were underway demonstrating greater treatment efficacy.

What is a Naltrexone implant?

Long-term sustained release naltrexone implants were first used clinically in 1997. Naltrexone implants are reasonably well tolerated as long as enough time has been left for the opiate substance of abuse to be entirely excreted from the body, between 5 and 10 days post use depending on the substance. Naltrexone can otherwise induce precipitated opiate withdrawal symptoms that may require hospital treatment.

The naltrexone implant pellet releases controlled amounts of naltrexone into the body, blocking the effect of opiates for three months. Naltrexone Implants, remove the risk of non-compliance found with oral forms of medication and by not thinking about taking a daily tablet, help to reduce cravings and allow a patient to move on from opiates.

How are naltrexone implants administered?

The administration of a naltrexone implant requires a minor surgical procedure. A very small incision is made in the lower abdomen in front of the hipbone, the implant inserted, and the wound closed with three or four stitches or the use of surgical glue. The procedure is performed under local anesthetic and takes about 20 minutes to perform. The patient is ready to leave within an hour of the procedure.

It is recommended that a patient have another implant three months after the first one. After the first six months, you can elect to have a further implant or choose to switch to naltrexone tablets. It is recommended that naltrexone be taken for at least 12 months after discharge.

Why take a naltrexone Implant?

Naltrexone helps prevent relapse. Most heroin addicts will have at least one relapse after getting ‘clean’. Research indicates that addicts who take naltrexone regularly have a better chance of staying clean than with any other treatment.

How effective is it?

Completely. Most addicts try using heroin soon after starting naltrexone. Once they realize that smoking or injecting even several grams of heroin has no effect, they don’t usually waste their money by trying again.

Is Naltrexone addictive??

Definitely not. Even after several months, there are no withdrawal symptoms if a patient stop’s suddenly.

Is it a new drug?

No. Oral Naltrexone has been used worldwide in a licensed tablet format for over 40 years. A number of variations exists in the presentation of the drug in unlicensed forms such as the implant and injection.

Who should think of taking Naltrexone?

Any opiate addict who wants to stop using opiates but who has never managed it for long, or at all (except in institutions) or who thinks that relying on will-power, NA or counselling alone will not work for them. Problem drinkers hoping to gain control rather than abstain from drinking.

Is counselling needed as well?

It is advised that all patients attend two or three times during the first month and at least every month or two for the next six months for addictions counselling. Some patients may need to come more often but if they stay clean for a few months and keep themselves occupied, many of their problems will probably resolve without much help. Clinicians like to involve family in treatment.

How often does it have to be taken?

Implants last 10-12 weeks.

Research in opiate patients:

Efficacy

The efficacy of the naltrexone implant has been examined in two large clinical trials. The first was conducted in Australia comparing the implant to oral naltrexone. In the study the patients and the research group were blinded to the treatment they were given, the subject receiving both the implant and an oral table made this possible. Half of the 70 subjects treated received a naltrexone implant and placebo tablets, while the other half received a placebo implant and naltrexone tablets. At the end of 6 month follow up 83% of the naltrexone implant subjects had not returned to regular heroin use, compared with 38% of the oral naltrexone tablet subjects.

The second study was carried out in Norway comparing naltrexone implants treatment to “usual care”. Usual care involved outpatient counseling, application to maintenance treatment programs, re-admission to detoxification or residential treatment programs, vocational counseling and social services. Subjects were randomized into the two treatments with 29 receiving naltrexone implants and 27 receiving usual care. At the end of the 6-month flow up period, subjects in the naltrexone implant group reported using heroin an average of 17.9 days and opiates 37.0 days as compared with the 63.6 days for heroin and 97.1 days for opiates in the subjects in usual care.

Safety

There is a limited amount of research focusing specifically on the safety of the naltrexone implant preparation. While naltrexone itself is generally considered as having a relatively well tolerated and has a good safety profile, the mode of administration is relatively new for this drug.

Biocompatibility and biodegradation

Biopsy and ultrasound have been used to examine the local biocompatibility and biodegradation of the implant. Studies found the implant was well tolerated with a localized tissue reaction, typically associated with the insertion of any foreign material, occurring in approximately 2% of patients. As the implants are slowly biodegraded, the tissue returned to normal and only a few of these tissue reactions require medical attention.

Fatal and non-fatal opiate overdoses

Following treatment with oral naltrexone, researchers and clinicians noted an increased risk on fatal and non- fatal opiate overdoses once the patients stopped the treatment. To ensure the implant wasn't associated with the same risks several study have examined rates of opiate overdose.

The largest study was a longitudinal follow up of 2155 patients treated with naltrexone implants and 2389 patients treated with oral naltrexone. The study found that mortality rates in patients treated with naltrexone implants were significantly less than patients treated with oral naltrexone (6.59 deaths per thousand patient years (ptpy) compared with 7.38 ptpy). Most notably, there was a reduction in death in the first 4 months following treatment in implant patients as compared to the oral (7.34 ptpy compared 26.28). This difference was largely attributable to high rates of opiate overdose mortality in the oral group (17.22 ptpy), while only a single opiate overdose death was noted in the first 4 months in the implant group (equating to 0.67 ptpy). Two other smaller studies comparing mortality in naltrexone implant patients and methadone or buprenorphine patients have found rates of mortality to be similar to both treatments. Additionally research has been shown that the rate of non-fatal opiate overdoses is reduced following treatment with naltrexone implants. A study examined 361 patients treated with naltrexone implants for opiate dependence.Hospital admissions for opiate overdoses were recorded for the 6 months prior to and 12 months following treatment. 17 incidents of opioid poisoning were identified in the 6 months prior to treatment. In contrast none were listed in the 6-month following treatment and only 2 were observed in the subsequent 6 months. Reductions in opiate and non- opiate overdoses following treatment have also been observed in Hulse (2005) and Ngo (2008).

Adverse Events:

Adverse events associated with the implant have been collected in a number of studies. A clinical review of patients treated in Queensland found that serious local tissue reaction or infection occurred each at 1% of the 200-implant treatments observed. Other complications included wound hematomas (1.0%), local itching or swelling (Rx topical steroids) (2.0%), several local lump (Rx oral steroids) (1.5%), removal for psychiatric indications (1.0%). Generally the implant is well tolerated with good outcomes in terms of opiate use.

Pharmacokinetics

A number of pharmacokinetics studies have been conducted, as well as studies in which pharmacokinetics has been a secondary outcome.

Naltrexone blood levels tend to be highly variable between and within patients, accounting for variations in recorded blood levels in different studies. Blood levels have been shown to remain above 2mg/ml (deemed therapeutic) for approximately 4 to 6 months.

Note

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