Prescribing information

Sixmo ▼ (buprenorphine) 74.2mg implant Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Each implant kit (one dose) contains 4 Sixmo implants, each containing 74.2mg buprenorphine, with 1 applicator. **Indications:** Substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment. **Dosage and Administration:** Treatment must be supervised by a healthcare professional experienced in the management of opioid dependence/addiction. Insertion/removal of the Sixmo implants must be performed by a physician competent in minor surgery specifically trained in the procedure. Posology: Sixmo should be used only in patients who are opioid tolerant. Each dose consists of four implants, for subcutaneous insertion in the inner side of the upper arm, to remain in place for 6 months. Remove by the end of the sixth month. Treatment with Sixmo: Sublingual buprenorphine should be discontinued 12 to 24 hours prior to insertion of implants. *Criteria for the use of supplemental sublingual buprenorphine:* Some patients may require occasional supplemental sublingual buprenorphine support to achieve full control of opioid withdrawal symptoms and cravings, e.g. at times of personal stress or crisis. Patients should not be provided with prescriptions for sublingual buprenorphine-containing products for as needed use. Instead, patients who feel the need for supplemental dosing should be seen and evaluated promptly. *Treatment discontinuation criteria:* Implant removal should be considered if: patient experiences severe or intolerable side effects (including severe precipitated withdrawal); signs of intoxication or overdose appear (miosis, lip cyanosis, sedation, bradycardia, hypotension, respiratory depression); patient experiences lack of efficacy, as evidenced by lasting withdrawal symptoms that require repeated management with sublingual buprenorphine. *Discontinuation:* Patients should be switched back to their previous dose of sublingual buprenorphine within 12 to 24 hours following implant removal. *Retreatment:* If continued treatment is desired at the end of the first six-month treatment cycle, a new set of 4 implants may be administered following removal of the old implants for one additional treatment cycle of six months. Experience of a second treatment cycle is limited. No experience of reimplantation beyond 12 months. Implants should be inserted in the inner side of the opposite upper arm as soon as possible after removal of the previous implants, preferably the same day. After one subcutaneous insertion in each arm (for a total of two treatments cycles), most patients should be transitioned back to their previous sublingual buprenorphine for continued treatment. *Elderly:* Not recommended in patients over 65 years, safety and efficacy not established. *Hepatic impairment:* Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Patients with mild to moderate hepatic impairment (Child-Pugh A and B) and patients who develop hepatic impairment while being treated with Sixmo, should be monitored for signs and symptoms of toxicity or overdose and if observed, remove implants and transition to a medicinal product that allows dose adjustment. *Renal impairment:* Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 mL/min). *Paediatric population:* Safety and efficacy in children under 18 years have not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; Severe respiratory insufficiency; Severe hepatic impairment; Acute alcoholism or delirium tremens; Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence; Patients with a history of keloid or hypertrophic scar formation as difficulties retrieving the subcutaneous implant are possible; Patients who have contraindications for MRI. **Warnings and Precautions:** *Treatment monitoring:* Patients should be cautioned they may experience somnolence, especially in the first week. Examine insertion site one week following implant insertion and regularly thereafter for signs of infection or any problems with wound healing, including evidence of implant extrusion as well as misuse or abuse. Recommended visit schedule is no less than once-monthly for continued counselling and psychosocial support. *Serious complications from insertion and removal of Sixmo implants:* Rare but serious complications, including nerve damage and migration resulting in embolism and death, may result from improper insertion. Additional complications may include local migration, protrusion, expulsion and implant breakage after insertion or during removal. Surgical intervention is necessary for removing an implant that has migrated. Subcutaneous insertion is essential to confirm proper placement by palpation. Implants placed too deeply (intramuscular or in the fascia) may lead to neural or vascular injury. Infection may occur at the site of the insertion or removal. Excessive palpation shortly after insertion may increase the chance of infection. Improper removal carries risk of infection and implant breakage. In rare cases, implants or partial implants could not be localized and were, therefore, not removed. *Expulsion of implant:* If spontaneous expulsion of the implant occurs after insertion - refer to the SmPC for the steps to be taken. *Misuse and diversion:* Sixmo is formulated as a diversion and abuse deterrent formulation. Nevertheless, it is possible to extract buprenorphine from the implant and all patients should be monitored for conditions indicative of diversion, or progression of opioid dependence and addictive behaviours suggesting the need for more intensive and structured treatment for substance use. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant abuse of buprenorphine and alcohol and other substances, especially benzodiazepines. *Dependence:* Chronic administration of buprenorphine produces dependence of the opioid type. If implants are not immediately replaced upon removal, patients should be maintained on sublingual buprenorphine (2 to 8 mg/day), as clinically indicated, until treatment is resumed. Patients who elect to discontinue treatment should be monitored for withdrawal syndrome, with consideration given to use of a tapering dose of sublingual buprenorphine. *Precipitation of opioid withdrawal syndrome:* Buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists before the effects of the full opioid agonist have subsided. Verify that patients have completed an appropriate induction period with sublingual buprenorphine or buprenorphine/naloxone, or are already clinically stable on buprenorphine or buprenorphine/naloxone before inserting implants. *Respiratory and central nervous system (CNS) depression:* Death due to respiratory depression has been reported while on buprenorphine, particularly when used in combination with benzodiazepines or other depressants such as alcohol or other opioids or when buprenorphine was not used according to prescribing information. If buprenorphine is administered to some non-opioid dependent individuals, who are not tolerant to the effects of opioids, potentially fatal respiratory depression may occur. Use with caution in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis). Buprenorphine may cause drowsiness, particularly when taken together with alcohol or CNS depressants (such as tranquilisers, sedatives or hypnotics). Prior to initiating therapy, review the patient's medical and treatment history, including use of non-opioid psychoactive substances. *Hepatitis and hepatic events:* Cases of acute hepatic injury (including fatal cases) have been reported with buprenorphine in opioid-dependent addicts. Hepatic risk factors and viral hepatitis status must be taken into consideration before prescribing Sixmo and during treatment. If a hepatic event is suspected, evaluate liver function and consider discontinuation of treatment. If treatment is continued, closely monitor hepatic function. *Hepatic impairment:* Patients with mild to moderate hepatic impairment should be monitored for signs and symptoms of toxicity, or overdose. *Treatment of acute pain during Sixmo therapy:* If patients need acute pain management or anaesthesia, treat with a non-opioid analgesic whenever possible. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under supervision, with particular attention to respiratory function. If opioid therapy is required as part of anaesthesia, patients should be continuously monitored in an anaesthesia care setting. Opioid therapy must be provided by healthcare professionals trained in the use of anaesthetic medicinal products and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation. *Renal impairment:* Renal elimination may be prolonged. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min). *CYP3A inhibitors:* Medicines that inhibit CYP3A4 may increase buprenorphine concentrations. Patients should be closely monitored for signs of toxicity if combined with potent CYP3A4 inhibitors. Patient's treatment history should be reviewed for concomitant use of CYP3A4 inhibitors prior to initiating treatment to determine suitability. *General opioid precautions:* Opioids may produce orthostatic hypotension in ambulatory patients and may elevate cerebrospinal fluid pressure, which may cause seizures. Should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure, as well as in patients with hypotension, prostatic hypertrophy or urethral stenosis. Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. Should be used with caution in patients with myxoedema, hypothyroidism or adrenal cortical insufficiency (e.g. Addison's disease). Opioids have been shown to increase intracholedochal pressure, and should be used with caution in patients with dysfunction of the biliary tract. Administer with caution to elderly or debilitated patients. Concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine. *Serotonin syndrome:* If concomitant treatment with other serotonergic agents (e.g. MAO inhibitors, SSRIs, SNRIs or tricyclic antidepressants) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases as it may result in serotonin syndrome, a potentially life-threatening condition. Symptoms may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, dose reduction or discontinuation should be considered depending on the severity of symptoms. *Skin:* Should be administered with caution in patients with a history of connective tissue disease (e.g. scleroderma) or history of recurrent methicillin-resistant *Staphylococcus aureus* infections. Contraindicated in patients with a history of keloid or hypertrophic scar formation at the site of the implant, as difficulties in retrieving the implant are possible. Effects on ability to drive and use machines: Sixmo may cause dizziness, somnolence or sedation especially at the start of treatment. Plasma concentrations of buprenorphine after insertion are highest during the first 24 to 48 hours. In particular, patients may experience somnolence for up to one week after insertion; therefore, they should be cautioned about driving or operating hazardous machinery especially during this time period. Before driving or operating hazardous machinery patients should be reasonably certain that Sixmo does not adversely affect their ability to engage in such activities. **Fertility, Pregnancy & Lactation:** *Pregnancy:* Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate. Consider neonatal monitoring for several days at the end of pregnancy, to prevent the risk of respiratory depression or withdrawal syndrome in neonates. Treatment with Sixmo should not be started in pregnant women. Not recommended during pregnancy and in women of childbearing potential not using contraception. If pregnancy occurs during treatment, the benefit to the patient should be weighed against the risk to the foetus. Other buprenorphine treatments/formulations are considered more appropriate in this situation. *Breast-feeding:* Buprenorphine and its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment. *Fertility:* There are no or limited data on effects of buprenorphine on human fertility. **Adverse Events include:** *Adverse events which could be considered serious:* Bronchitis, pharyngitis, cellulitis, peritonsillar abscess, urinary tract infection, neutropenia, depression, drug dependence, syncope, depressed level of consciousness, atrial flutter, bradycardia, hypertension, dyspnoea, respiratory depression, haematochezia, erectile dysfunction, device protrusion or expulsion, platelet count decreased, blood bilirubin increased, migration of implanted drug, device breakage. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants. *Other Common adverse events:* Viral infection, infection, influenza, rhinitis, decreased appetite, insomnia, anxiety, hostility, nervousness, paranoia, headache, dizziness, somnolence, hypertonia, mydriasis, palpitations, hot flush, vasodilation, cough, constipation, nausea, vomiting, diarrhoea, abdominal pain, gastrointestinal disorder, tooth disorder, hyperhidrosis, bone pain, myalgia, fatigue, chills, asthenia, pain, implant site haematoma, implant site pain, implant site pruritus, implant site haemorrhage, implant site erythema, implant site scar, chest pain, malaise, drug withdrawal syndrome, procedural pain, procedural site reaction, alanine aminotransferase increased. See SmPC for details of other adverse events. **Presentation and Price:** 1 pack (1 x 4 implants for injection) £1,438.20 **Legal Category:** POM (CD Schedule 3) **Further information is available from:** Accord-UK Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS. **Marketing Authorisation Numbers:** EU/1/19/1369/001, PLGB 16046/0027 **Date of PI Preparation:** August 2021 **Document number:** UK-02539

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Accord-UK LTD on 01271 385257 or email medinfo@accord-healthcare.com.