

Milnacipran hydrochloride (mil) uses in medicine



**ASSIGN
BUSTER**

Milnacipran hydrochloride (MIL) is a selective serotonin and norepinephrine reuptake inhibitor. It was originally developed and manufactured by Pierre Fabre Medicament in France, and was approved in that country as an antidepressant in 1997 [1]. It has since been approved for this indication in multiple countries and currently marketed for this indication in over 45 countries worldwide including several European countries. Cypress Bioscience bought the exclusive rights for approval and marketing of the drug for fibromyalgia purpose in the United States and Canada in 2003 from the manufacturer Pierre Fabre Laboratories [2-3].

In January 2009 the U. S. Food and Drug Administration (FDA) approved MIL only for the treatment of fibromyalgia, making it the third medication approved for this purpose in the United States [4].

Some of the drug information and properties are listed below:

2. 1 Physical and chemical properties

Chemical name: MIL is chemically designated as (1R, 2S)-rel-2(Amino-methyl)-N, N-diethyl-1-phenyl-cyclopropanecarboxamide hydrochloride and its structure is shown in Figure 2. 1.

Synonyms: F-2207; Ixel; Toledomin; Dalcipran; Milnacipran Hydrochloride.

Empirical formula: C₁₅ H₂₂ N₂ O. HCl

Molecular weight: 282. 8

CAS No.: 101152-94-7

Melting point: 179°C

Physical description: MIL is a white to off-white, odourless, crystalline powder.

Dissociation constant (pKa): 9.65

Permeability coefficient (Log P): 1.42

Solubility : It is freely soluble in aqueous buffers over the entire physiological pH range. It is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and sparingly soluble in diethyl ether [5-6].

BCS class: Class I, highly soluble and highly permeable drug.

2.2 Pharmacological properties

Mechanism of Action

Milnacipran blocks 5-HT and norepinephrine (NE) reuptake into the neuron, thereby increasing 5-HT and NE extracellular concentrations. This activates 5-HT and NE auto and heteroreceptors culminating in a decreasing 5-HT and NE neuronal firing rates, synthesis, and release. On Chronic use MIL continues to block 5-HT and NE transporters without desensitization, but 5-HT and NE auto- and heteroreceptors are desensitized and thus, down regulated. Firing rates of 5-HT and NE return to normal, and the amount of 5-HT and NE released per nerve impulse is increased [7].

MIL has no significant affinity for α - and β -adrenergic, muscarinic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazepine, or γ -

aminobutyric acid (GABA) receptors. MIL has no significant affinity for Ca^{2+} , K^{+} , Na^{+} and Cl^{-} channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase [8-9].

One of the main differences between the various antidepressants and MIL is its equal preference and activity on the uptake of NE and 5-HT. The exact mechanism of the central pain inhibitory action and effectiveness in fibromyalgia symptom are unknown in Humans [10-11].

2. 3 Therapeutic Indications

Treatment of depression

Major Depression, also known as major depressive disorder or unipolar depression, is a highly debilitating disorder that has been estimated to affect up to 21% of the world population [12]. It is a CNS disorder characterised by a combination of symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy pleasurable activities [7, 12].

Despite the advances in the treatment of depression with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), there continue to be many unmet clinical needs with respect to both efficacy and side effects. These needs range from efficacy in treatment resistant patients, to improved onset, to reductions in side effects such as emesis or sexual dysfunction. To address these needs, there are numerous combination therapies and novel targets that have been identified that may demonstrate improvements in one or more areas [12].

Management of Fibromyalgia

<https://assignbuster.com/milnacipran-hydrochloride-mil-uses-in-medicine/>

Fibromyalgia (FM) is a complex syndrome characterized by chronic musculoskeletal pain which is often accompanied by multiple other symptoms, including fatigue, sleep disturbances, decreased physical functioning, and dyscognition. Due to these multiple symptoms, as well as high rates of comorbidity with other related disorders, patients with FM have a reduced quality of life. The reduced serotonin and norepinephrine levels observed in patients with FM suggest that medications which increase the levels of these neurotransmitters, such as serotonin and norepinephrine reuptake inhibitors (SNRIs), may have clinically beneficial effects in FM and other chronic pain conditions. MIL is an SNRI that has been approved for the management of FM [8, 13]. MIL was viewed as a wonderful new weapon in the fight against both depression and pain.

Treatment of Lupus

Recent studies proved that MIL is also useful against lupus. Lupus is a chronic autoimmune disease in which the immune system turns against the body and harms healthy cells and tissues. It is a rheumatic disease which can affect many parts of the body including the joints, skin, kidneys, lungs, heart or brain. Some of the most common symptoms include extreme fatigue, painful or swollen joints, unexplained fever, skin rashes, and kidney problems. Scientific evidence indicates that lupus is caused by a combination of genetic and environmental factors. Lupus is characterized by periods of increased or intensified disease activity, called flares [14-15].

Tolerability and side effects

MIL has demonstrated numerous adverse reactions in human clinical trials with tolerability decreasing with an increasing dose. In the placebo controlled trials in patients with fibromyalgia, the most frequent spontaneously reported adverse events were as follows: nausea, palpitations, headache, constipation, increased heart rate and hyperhidrosis, vomiting, and dizziness [16]. Discontinuation due to adverse reactions was generally more common among patients treated with 200 mg/day compared to 100 mg/day. The adverse effects can originate from the fluctuation in the plasma drug concentrations of an active substance following administration and subsequent metabolism and/or elimination from the body. Most of the reported adverse events were reduced or disappeared with the discontinuation of treatment [17].

2. 4 Pharmacokinetics

The pharmacokinetic profile of MIL is as summarized in Table 2. 1 [1, 5].

Absorption

MIL is well-absorbed after oral administration. Absolute bioavailability is about 85-90 %. It is not affected by food intake. The peak plasma concentration is about 120 ng/ml achieved in 2 hours after a single 50 mg dose. Inter-subject variability is low . Plasma concentrations are linearly proportional with dose over the range of single acute doses of 25 to 200 mg as shown in Table 2. 2 [1, 2].

Distribution

Protein binding is low (13%) and not saturable. The volume of distribution of MIL is about 5 litre/kg with a total clearance of about 40 litre/hour. Renal and non-renal clearances are equivalent [1].

Metabolism

MIL is metabolized mainly by conjugation (Glucoronisation). Active metabolites have been found at very low levels without clinical relevance. Cytochrome P450 2D6 is involved in the metabolism of many psychotropic drugs and its inhibition is frequently a cause of drug-drug interactions. This enzyme has no impact on the metabolism of MIL and no oxidative metabolites of MIL have been detected in humans [1-3].

The pharmacokinetics of MIL are not modified in subjects who are deficient in the CYP2D6 isoenzyme (slow sparteine-like metabolisers). Furthermore, MIL does not interfere in-vivo with other isoenzymes of cytochrome P450 [1, 18].

Elimination

Plasma elimination half-life is about 8 hours. Elimination occurs mainly via the kidney with tubular secretion of the product in unchanged form. After repeated doses, MIL is totally eliminated in 2 to 3 days after termination of therapy. The liver and kidneys are both involved in the elimination of MIL as illustrated by renal and non-renal clearances with values of 23.8 ± 7.3 and 16.4 ± 3.1 l/h, respectively. This balance between renal and non-renal clearances may be an advantage in patients presenting with moderate renal insufficiency [3, 5].

2. 5 Dosage and administration

<https://assignbuster.com/milnacipran-hydrochloride-mil-uses-in-medicine/>

The recommended dose titration schedule for MIL is 12.5 mg once on Day 1, then 12.5 mg twice a day on Days 2-3, and then 25 mg twice a day on Days 4-7, and then 50 mg twice a day after Day 7. Recommended maintenance dose is 50 mg twice daily. In clinical trials, MIL was evaluated with a dose titration schedule. The daily dose may be increased to 200 mg (or 100 mg twice a day) based on individual response. Dosing should be adjusted in patients with severe renal impairment ($\text{CrCl} < 29 \text{ ml/min}$) with a reduced maintenance dose to 25 mg twice a day. Following extended use, MIL should be tapered and not abruptly discontinued. MIL may be taken with or without food, but taking it with food may improve tolerability [4, 13].

2.6 Marketed formulations

There are various brands of MIL available with dose of 12.5 mg, 25 mg, 50 mg and 100 mg immediate release tablets or capsules as shown in Table 2.3 [19-21].