

FULL PRESCRIBING INFORMATION
(F-PI)



Antifibrotic antiinflammatory drug.
Adjuvant in the treatment of fibrosis and inflammation associated with Liver Cirrhosis and Pulmonary Fibrosis.

1. GENERIC NAME

Pirfenidone

2. BRAND NAME

KITOSCELL LP™

3. DOSAGE FORM AND FORMULATION

SUSTAINED RELEASE TABLETS

Each TABLET contains:

Pirfenidone	100 mg	200 mg	300 mg	600 mg
Vehicle qs	1 tablet	1 tablet	1 tablet	1 tablet

4. THERAPEUTIC INDICATIONS

For use in patients with Hepatic Inflammation and Fibrosis. Should also be indicated in the treatment of Pulmonary Fibrosis.

As a drug that selectively modulates cytokines such as TNF- α , TGF- β , PDGF and VEGF, as well as other cytokines, KITOSCELL LP™ Tablets are indicated in conditions that occur with chronic fibrosis associated with tissue damage, such as: Advanced liver fibrosis or pulmonary fibrosis, where required to prevent, reduce, inhibit or reverse fibrotic lesions.

Treatment with KITOSCELL LP™ Tablets should be initiated and supervised by specialist physicians with experience in diagnosing and treating Hepatic and/or Pulmonary Fibrosis.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The active ingredient of KITOSCELL LP™ Tablets is Pirfenidone [1-phenyl-5-methyl-2-(1H)-pyridone], a very small synthetic, non-peptide chemical molecule, with a molecular weight of 185.2. It acts as a selective regulator of cytokines, an action that affords it specific antifibrotic and antiinflammatory properties.

KITOSCELL LP™ Tablets prevent the formation of tissue fibrosis, reduce the progress of processes concurrent with fibrosis and removes them because it acts as a potent modulator of the specific effects of several human cytokines (TNF- α , TGF- β , PDGF and VEGF, among other cytokines), which are directly responsible

for the process of chronic inflammation, overproduction of fibrotic tissue and the proliferation of fibroblasts. In addition, KITOSCELL LP™ Tablets reduces the number of inflammatory cells.

All of these effects are produced because it acts inside the cell through a molecular mechanism, in a place located inside the nucleus of the cell. The exact site of the action of KITOSCELL LP™ Tablets has been the subject of extensive research by molecular biology specialists, and it has been determined that the action of KITOSCELL LP™ Tablets takes place inside the cell nucleus.

Its action might be said to be at the transcriptional level, at the place where an interface occurs between the signals of specific genes or groups of genes, which are being transmitted to the process by NF κ B and AP-1 type proteins, to initiate or influence the transcription process. As is known, almost all tissue regeneration processes are dependent on these proteins, which increase in the event of tissue injuries.

In due course, these transmissions regulate mitotic events (GO to GS) and exert control via the kinins, signaling to the genes that influence the transcription process, and they are crucial for implementing numerous biochemical processes of synthesis, which are necessary to maintain homeostasis (physiological and biochemical) of the cytoplasm and the nucleus of the cell.

They also act on the synthesis and/or storage of a variety of biochemical compounds that are released to complement or regulate other cells in the adjacent medium, and the induction of cell proliferation and the formation of interstitial collagen or amyloid matrix.

The cytokines become monitors of events related with the cell, tissue or organic damage. They are continually exercising vigilance over the cell proliferation and the cellular biochemical processes required to repair the cell or tissue damage. Once again, the proteins NF κ B and AP-1 are the common pathways for the signals of these cytokines, which are involved in the normal tissue repair process.

Following the physiopathology of the cytokines, these are involved in the formation and development of fibrosis and in increased collagen deposits. These peptides are released by cells such as platelets, monocytes, lymphocytes and neutrophils in the capillaries of the site where the injury or the inflammatory and fibrotic process occurred. These changes cause interstitial thickening and loss of the tissue architecture.

When high concentrations of these cytokines are released at the sites where damage has occurred, large amounts of proteins (transcription factors such as NFκB and AP-1) are synthesized and released by a significant variety of cells around the damaged area. If those elevated levels fail to return to normal concentrations, they will lead to chronic inflammation and undesirable events such as:

- Alterations in tissue regeneration, which can manifest as scars or fibrotic lesions.
- Alteration in the production of molecules (collagen, fibronectin, amyloid or sarcoid material, etc.).
- Formation of autacoids that cause additional toxicity and cell death.

These events link with the mechanism of action of KITOSCELL LP™ Tablets because it functions at the level of the NFκB and AP-1 proteins; KITOSCELL LP™ Tablets has consistently shown to exert a marked modulating action on the key cytokines involved in the inflammatory-fibrotic process (mainly TNF-α, TGF-β, FGF, PDGF and VEGF).

Additionally, KITOSCELL LP™ Tablets have been demonstrated to modulate TGF-β on multiple levels:

- Reducing the transcription of TGF-β mRNA, which leads to a reduced expression of the final protein of TGF-β.
- Directly inhibiting Furin, which is a proprotein convertase.

These actions modulate the balance in the production of MMPs, enzymes which break down the fibrotic tissue in situations where there is an excessive accumulation of fibrosis.

Molecules of KITOSCELL LP™ Tablets cross through the cell wall and because of their size, they penetrate through to the nucleus without involving a peptide or protein carrier. Moreover, molecules of the KITOSCELL LP™ Tablets do not apparently depend on specific receptors to be introduced into the target cell. They are also not dependent on the formation of cascades triggered or caused by stimulation of the receptors of the cell membrane, but instead by actions of molecular modulation produced directly on the genome at the sites of the cell nucleus.

Data obtained from studies in animal models in vivo, in human fibroblasts and other mesenchymal cells in vitro, suggest that KITOSCELL LP™ Tablets can be considered a therapeutic agent for the prevention and/or treatment of many diseases with a common factor: fibrosis. These include: Advanced Liver Fibrosis, Post-surgical Adhesions, Kidney Fibrosis, Pulmonary Fibrosis, Hypertrophic Scars and others. This is because KITOSCELL LP™ Tablets selectively modulate or inhibit the harmful activity of proinflammatory and profibrotic human cytokines, which are directly responsible for exacerbating the chronic inflammatory and fibrotic process, as well as the excessive proliferation of fibroblasts or cells related with fibrosis. Consequently, KITOSCELL LP™ Tablets are considered an effective therapeutic resource to:

- Prevent the formation of fibrotic lesions (including scars, adhesions, etc.),
- Reduce preexisting fibrotic advancement, and
- Revert fibrotic lesions.

As it is a non-protein molecule, there is no evidence of the formation of antibodies against it, which minimizes the possibility of creating any immunogenic reaction.

Studies conducted for up to 44 months for the treatment of Idiopathic Pulmonary Fibrosis showed that the group of patients treated with Pirfenidone improved its lung function values. For example, there was a demonstrable increase in the percentage of Forced Vital Capacity, Forced Expiratory Volume in 1 second, Total Lung Capacity and Diffusing Capacity for Carbon Monoxide, compared with patients in the control group. It also lowered the number of acute exacerbations and a decrease was also found in the progression of Pulmonary Fibrosis.

The results of studies for the treatment of Hepatic Fibrosis with Pirfenidone showed an improvement in the quality of life in most patients treated for 24 months with KITOSCELL LP™ Tablets. Furthermore, according to the Child-Pugh classification system, it was also observed that in 81% of patients there was no disease progression and their ALT levels were significantly improved.

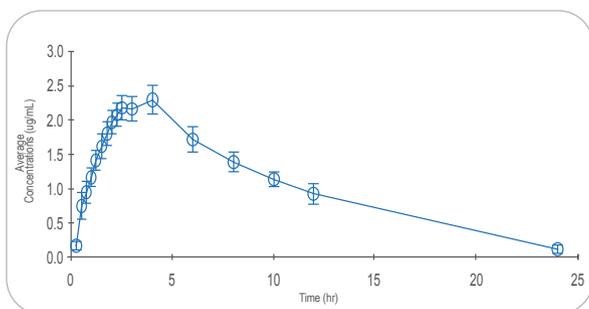
Studies also showed the direct action on fibrosis. 70% of patients assessed after 24 months of treatment with Pirfenidone showed a marked histological improvement in the hepatic necroinflammatory score (equal to or greater than 3 points) as measured by the modified Knodell index. Similarly, 55% of patients showed a decrease in the degree of fibrosis, according to the Ishak grading scale.

Furthermore, Bioavailability and Pharmacokinetics studies showed the following:

Following administration of a single oral dose of pirfenidone via 600 mg sustained-release tablets in healthy male subjects, it was shown that the kinetic behavior of KITOSCELL LP™ Tablets in this dosage form was as follows:

Pharmacokinetic Parameter	Average Formulation of Pirfenidone
AUC ₀₋₁ (µg/ml)	22.787
AUC ₀₋₂₄ (µg/ml)	30.022
Vd/F (ml)	178165.969
Cl/F (ml/hr)	26379.200
C _{max} (µg/ml)	2.469
Ke (hr)	0.220
T _{1/2} (hr)	10.798
T _{max} (hr)	3.250

Plasma concentrations µg/ml vs time



Based on these results, it is demonstrated that the bioavailability of the dosage form is 1.2 µg/ml in 1 hour, and the maximum concentration is 2.4 µg/ml, which is attained in 4 hours. According to these results we can establish that the pharmacological activity of the dosage form (sustained-release tablets 600 mg) maintains a therapeutic effect for up to 12 hours, before reaching the threshold of the plasma concentration at which it does not induce a biological response.

Pirfenidone binds to plasma proteins, chiefly serum albumin. The total average binding percentage varies between 50% and 58% at the concentrations observed in clinical trials (between 1 and 100 µg/ml).

The apparent average volume of distribution, orally, is roughly 70 liters, indicating that there is modest distribution of Pirfenidone in the tissues.

In vitro metabolic studies with liver microsomes indicate that approximately 48% of Pirfenidone is metabolized primarily by CYP1A2 and other CYP isoenzymes, such as CYP2C9, 2C19, 2D6 and 2E1, which contribute less than 13%. In vitro and in vivo studies carried out to date have not detected any activity of the main metabolite (5-carboxy-pirfenidone), even at concentrations or doses well above those associated with the activity of Pirfenidone itself.

Clearance of KITOSCELL LP™ Tablets taken orally appears to be modestly saturable. Approximately 80% of the Pirfenidone dose administered orally is eliminated in the urine within 24 hours of administration. Most of the Pirfenidone is excreted in the form of the metabolite 5-carboxy-pirfenidone (more than 95% of which is recovered). Less than 1% of the Pirfenidone is excreted intact in the urine.

6. CONTRAINDICATIONS

KITOSCELL LP™ Tablets is contraindicated in patients with allergies to formula’s components. Concomitant use with Fluvoxamine is contraindicated. If the patient is already taking Fluvoxamine, treatment with this medication must be suspended before starting treatment with KITOSCELL LP™ Tablets.

Other treatments which inhibit CYP1A2 or other CYP isoenzymes that may be involved in the metabolism of KITOSCELL LP™ Tablets (CYP2C9, 2C19 and 2D6) should also be avoided. Terminal liver disease. Severe renal insufficiency (CrCl < 30 ml/min) or terminal kidney disease requiring dialysis.

7. GENERAL PRECAUTIONS

Exposure to direct sunlight must be avoided or minimized during treatment with KITOSCELL LP™ Tablets owing to very occasional reports of transient photosensitivity dermatitis.

Patients must be directed to use sunscreen and clothing to protect them from sun exposure daily, and to avoid other medications that are known to cause photosensitivity.

The presence of dizziness and tiredness has been described in some patients treated with Pirfenidone.

Caution should be exercised in patients with hepatic insufficiency, as elevated ALT and AST of up to three times above the normal upper limit have been described as a result of treatment with KITOSCELL LP™ Tablets. This is why liver function tests are recommended before initiation of treatment and subsequently every month during the first 6 months and then every 3 months thereafter. Depending on the laboratory results, the doctor may recommend adjusting the dose.

The administration of KITOSCELL LP™ Tablets is not recommended in patients with severe renal insufficiency severe (CrCl < 30 ml/min) or terminal kidney disease.

8. RESTRICTIONS DURING PREGNANCY AND/OR LACTATION

There is no experience with the use of KITOSCELL LP™ Tablets in women during pregnancy or the lactation period. For that reason, its administration in these periods is at the discretion of the attending physician. In studies in laboratory animals, Pirfenidone and/or its metabolites cross the placenta and can accumulate in the amniotic fluid. In rats given high doses (≥ 1000 mg/kg per day), the gestation period was prolonged and fetal viability decreased. As a precaution, it is recommended that KITOSCELL LP™ Tablets be avoided during pregnancy.

The use KITOSCELL LP™ Tablets during lactation is a decision for the attending physician, since it is unknown whether Pirfenidone or its metabolites are excreted in breast milk. In laboratory animals it has been found that Pirfenidone or its metabolites are excreted in the milk.

9. SECONDARY AND ADVERSE REACTIONS

Its secondary or side effects have been of small clinical significance and transient. At therapeutic doses, gastrointestinal symptoms have been reported such as stomach pain, nausea or dizziness, which decrease if ingested after meals. Occasionally, photosensitivity dermatitis has occurred. These side effects have not merited discontinuing or withdrawing treatment because when they have occurred, they disappear within two to three weeks.

Some studies with other dosage forms have shown some adverse reactions such as:

Infections

- *Upper respiratory tract infection*
- *Urinary tract infection*

Metabolism disorders

- *Weight loss; anorexia; loss of appetite*

Nervous System Disorders

- *Insomnia*
- *Dizziness*
- *Headache*
- *Somnolence*
- *Dysgeusia*

Vascular disorders

- *Hot flashes*

Respiratory disorders

- *Dyspnea*
- *Cough*

Gastrointestinal disorders

- *Dyspepsia*
- *Nausea*
- *Diarrhea*
- *Gastroesophageal reflux disease*
- *Vomiting*
- *Bloating*
- *Abdominal pain*
- *Constipation*
- *Flatulence*
- *Elevated liver enzymes ALT, AST, GGT.*

Integumentary System Disorders

- *Photosensitivity causing cutaneous eruption*
- *Pruritus*
- *Erythema*
- *Dry skin*

Musculoskeletal disorders

- *Myalgia*
- *Arthralgia*
- *General disorders*
- *Asthenia*

10. DRUG INTERACTIONS AND OTHER KINDS OF INTERACTIONS

Concomitant use of some drugs that are moderate CYP1A2 inducers may, theoretically, reduce the plasma concentrations of Pirfenidone as Pirfenidone is metabolized primarily by CYP1A2. In vitro studies indicate that about 48% of Pirfenidone is metabolized by CYP1A2 and other CYP isoenzymes metabolize less than 13%.

It is not recommended to consume grapefruit juice simultaneously with KITOSCELL LP™ Tablets as grapefruit can cause CYP1A2 inhibition.

It is recommended that a thorough assessment of treatments in combination with Fluvoxamine or other potent inhibitors of CYP1A2 or of other CYP isoenzymes, such as: Amiodarone, Fluconazole, Chloramphenicol, Fluoxetine, Paroxetine, Ciprofloxacin, Rifampicin or Propafenone.

The use of KITOSCELL LP™ Tablets together with tobacco must also be assessed since the latter may induce the production of liver enzymes, thereby increasing the clearance of KITOSCELL LP™ Tablets and consequently reducing its effectiveness.

11. ALTERATIONS AND LABORATORY TESTS

KITOSCELL LP™ Tablets may alter some enzymes such as ALT and AST. For this reason, liver function tests are recommended before beginning treatment and subsequently every month for the first 6 months and then every 3 months. Depending on the laboratory results, the doctor may recommend adjusting the dose.

12. PRECAUTIONS AND RELATIONSHIP WITH EFFECTS OF CARCINOGENESIS, MUTAGENESIS, TERATOGENESIS AND ON FERTILITY

Available information indicates that KITOSCELL LP™ Tablets are not considered to be teratogenic, carcinogenic or mutagenic according to the Ames test. There are no data indicating that it could affect reproductive capacity.

13. DOSE AND ROUTE OF ADMINISTRATION

Route of administration: Oral.

Adults: 1200 mg - 2400 mg per day, divided into doses every 12 hours

Children able to swallow tablets from 12 years of age: 600 mg - 1200

mg per day, divided into doses every 12 hours.

Weighted Dose: By Body Area: 250 mg - 500 mg/dose per m² of body area, twice daily.

The tablet can be divided, when required, based on the recommended dosage.

Preferably ingest 20 to 30 minutes after food. In patients with severe hepatic insufficiency, aminotransferases should be monitored and the dose should be adjusted according to the values of the study under the following recommendation:

- *Patients with ALT aminotransferases within normal limits: maintain the dose.*
- *Patients with increased ALT aminotransferases to 3-5 times above the normal limit: any medications that may alter the results of the study must be suspended and the patient closely monitored, as determined by the attending physician. The dose of KITOSCELL LP™ Tablets can remain unchanged or be reduced for a while, returning to the maximum dose of progressively in phases.*
- *Patients with increased aminotransferases by more than 5 times or less than 5 times accompanied by hyperbilirubinemia or severe symptoms of Advanced Liver Failure: it is recommended that treatment be discontinued permanently.*

Must be prescribed by a specialist physician.

14. MANIFESTATIONS AND HANDLING OF OVERDOSES OR ACCIDENTAL INGESTION

There is limited clinical experience with overdoses. Some clinical studies where high doses of Pirfenidone was administered reported mild, transient reactions consistent with the adverse reactions most frequently observed with Pirfenidone.

If overdose is suspected, provide medical assistance with monitoring of vital signs and close observation of the patient's clinical situation.

15. PRESENTATION

Bottle with 30, 60 or 90 tablets of 100 mg, 200 mg, 300 mg and 600 mg.

16. STORAGE RECOMMENDATIONS

Store in a dry place at room temperature.

17. PROTECTION LEGENDS

Must be prescribed by a specialist physician.

Keep out of reach of children.

For sale by medical prescription only.

Literature exclusively for doctors.

Not to be used during pregnancy, lactation, or in children under 12 years of age.

Report suspected adverse reactions to the following email address:
farmacovigilancia@cofepris.gob.mx

18. NAME OF LABORATORY

Made in Mexico by:

Grupo Medifarma S.A. de C.V.

Matamoros No. 9,

Col. Centro, C.P. 62550,

Jiutepec, Morelos, Mexico.

19. REGISTRATION NUMBER OF THE MEDICATION

Reg. No. 154M2013 SSA IV



CELL PHARMA

Innovation and Efficacy on
Anti-fibrotic Therapy

