SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

BREXIN TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:
piroxicam β-cyclodextrin 191.2 mg, (equivalent to piroxicam 20 mg).
Excipient with known effect: lactose monohydrate, sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piroxicam is indicated for symptomatic relief of osteoarthritis rheumatoid arthritis or ankylosing spondylitis. When an NSAID is indicated piroxicam should be considered as a second line option. The decision to prescribe piroxicam should be based on an assessment of the individual's patient overall risk.

4.2 Posology and method of administration

Posology

The prescription of piroxicam should be initiated by physicians with experience in the diagnosis and treatment of patients with inflammatory or degenerative rheumatic diseases.
The maximum recommended daily dose is 20 mg.
Undesirable effects may be minimised by using the minimum effective dose for the shortest duration of treatment necessary to control symptoms. The benefit and tolerability of treatment should be reviewed within 14 days. If it is considered necessary to continue treatment, this should be accompanied by frequent review.
Given that piroxicam has shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

Paediatric population

Dosage and indications in children have not been established yet.

Elderly

In elderly patients, the posology must be carefully established by the physician who will have to consider a possible reduction of the dosage indicated above.

Method of administration

BREXIN should be administered once daily.

1 tablet per day. The tablet is for oral use. The score on the tablet is intended to

ease the splitting and swallowing of the tablet and not to divide it into equal parts. To split the tablet, put it on a flat surface with the score facing upwards. Press gently with your thumb to break the tablet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of gastrointestinal ulceration, bleeding or perforation.
- History of gastrointestinal disorders that predispose to bleeding disorders such as ulcerative colitis, Crohn's disease, gastrointestinal cancer or diverticulitis.
- Patients with active peptic ulcer, inflammatory gastrointestinal disorders or gastrointestinal bleeding. Patients with gastritis, dyspepsia, severe hepatic or renal disorders, moderate or severe heart failure, severe hypertension, severe blood changes or haemorrhagic diathesis. Concomitant use of other NSAIDs, including COX-2 selective inhibitors and acetylsalicylic acid administered at analgesic doses. Concomitant use of anticoagulants. History of severe allergic drug reactions of any type, especially skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Previous skin reactions (regardless of severity) to piroxicam, other NSAIDs and other medicines.
- Known or suspected pregnancy, during breastfeeding or the use in children (see section 4.6).
- There is a potential for cross-sensitivity with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs. This product should not be given to patients in whom acetylsalicylic acid or other non-steroidal anti-inflammatory drugs have induced symptoms of asthma, rhinitis, nasal polyposis, angioedema or urticaria.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration of treatment necessary to control symptoms.
The clinical benefit and tolerability of the treatment should be re-evaluated regularly and treatment should be immediately discontinued at the first appearance of skin reactions or significant gastrointestinal events.

Gastrointestinal (GI) effects, risk of gastrointestinal ulceration, bleeding, and perforation.
NSAIDs, including piroxicam, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or colon, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.
NSAID exposure of both short and long duration carries an increased risk of severe gastrointestinal events. Evidence from observational studies suggests that, compared to other NSAIDs, piroxicam may be associated with a high risk of severe gastrointestinal toxicity.
Patients with significant risk factors for severe GI events should be treated with piroxicam only after careful consideration (see below and section 4.3).
The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered (see section 4.2).

Severe gastrointestinal complications
Identification of at-risk subjects

The risk for developing serious gastrointestinal complications increases with age. Being aged over 70 years is associated with a high risk of complications. Using this medicine in patients older than 80 years should be avoided.
Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs), anticoagulants such as warfarin or antiplatelet agents such as low-dose acetylsalicylic acid are at increased risk of severe gastrointestinal complications (see below and section 4.5). As with other NSAIDs, the use of piroxicam in combination with gastro-protectants agents (e.g. misoprostol or proton pump inhibitors) must be considered for these at-risk patients.
Patients and physicians should be alert for signs and symptoms of gastrointestinal ulceration and/or bleeding during piroxicam treatment. Patients should be asked to report any new or unusual abdominal symptom that may appear during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately and an additional clinical evaluation and alternative treatment should be considered.

Cardiovascular and cerebrovascular effects

Suitable monitoring and instructions are necessary in patients with a history of hypertension and/or congestive heart failure, as fluid retention and oedema have been reported in association with NSAID treatment.
Clinical studies and epidemiological data indicate that the use of some NSAIDs (especially at high doses and for long-term treatment) may be associated with a moderate increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). There are not enough data to exclude such a risk for piroxicam.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should be treated with piroxicam only after careful evaluation. Similar considerations should be made before starting long-term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
Piroxicam, like other NSAIDs, reduces platelet aggregation and prolongs bleeding time; this characteristic must be taken into account when blood tests are performed and when the patient is concomitantly treated with other platelet aggregation inhibitors.
Patients with impaired renal function should be periodically monitored, as in these patients the inhibition of prostaglandin synthesis caused by piroxicam may result in a severe decrease in renal perfusion that may lead to acute renal failure. In this regard, elderly patients and patients treated with diuretics should be considered as at risk.
Dehydrated patients are at risk of impairment of renal function.
Caution should also be taken in patients with impaired hepatic function. It is also recommended to regularly monitor their clinical and laboratory parameters, especially in cases of prolonged treatment.
Due to its interaction with arachidonic acid metabolism, the drug may induce bronchospasms and possibly shock and other allergic phenomena in asthmatic and predisposed patients.

As some ocular changes have been observed during therapy with NSAIDs, regular ophthalmological examinations are advised during prolonged treatment.

It is also recommended to frequently check blood glucose levels in diabetic patients and prothrombin time in patients concomitantly receiving anticoagulant treatment with dicoumarol derivatives.

Skin reactions

Evidence from observational studies suggests that piroxicam may be associated with a higher risk of serious skin reactions compared to other non-oxicam NSAIDs.
In association with the use of BREXIN, the following , potentially fatal skin reactions have been reported including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
Patients should be advised of and closely monitored for any signs and symptoms of skin reactions. Patients appear to be at highest risk of appearance of SJS and TEN during the initial weeks of treatment. Treatment with BREXIN should be discontinued at the first appearance of symptoms and signs of SJS or TEN (.e.g. progressive skin rash, often with blisters and mucosal lesions).
The best results in the management of SJS and TEN are achieved with early diagnosis and the prompt discontinuation of therapy whatever the suspect medicine. Early discontinuation is associated with a better prognosis.

Patients developing SJS or TEN with the use of BREXIN, should never be treated with BREXIN again.

Cases of fixed drug eruption (FDE) have been reported with piroxicam. Piroxicam should not be reintroduced in patients with a history of FDE associated with piroxicam. A potential cross-reaction with other oxicams may occur.

Hepatic effects

Piroxicam may cause fatal hepatitis and jaundice. Although these reactions are rare, taking piroxicam must be discontinued if the liver function tests are outside the normal range or worsen, if clinical signs and symptoms appear compatible with liver disease or in the event of systemic manifestations (e.g. eosinophilia, skin rash etc.).

Poor metabolizers of CYP2C9 substrates

In patients who are known or suspected poor metabolizers of CYP2C9 based on their medical history/experience with other CYP2C9 substrates, piroxicam should be administered with caution because excessively high plasma levels may appear due to the reduced metabolic clearance (see section 5.2).

The use of piroxicam, as with any prostaglandin synthesis or cyclo-oxygenase inhibitor, is not recommended in women planning to start a pregnancy.

The administration of piroxicam should be discontinued in women with fertility problems or who are undergoing fertility investigations.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol (23 mg) of sodium per tablet, so it is essentially sodium-free.

4.5 Interactions with other medicines and other forms of interaction

Acetylsalicylic acid or other NSAIDs: As with other NSAIDs, the use of piroxicam together with acetylsalicylic acid or other NSAIDs, including other piroxicam formulations, must be avoided, since data are inadequate to show that such combinations produce greater improvement than that achieved with piroxicam alone; moreover, the potential for adverse reactions is increased (see section 4.4).
Human studies have shown that the concomitant use of piroxicam and acetylsalicylic acid reduces the plasma piroxicam concentration to about 80% of the usual value (see section 4.3).
Piroxicam interacts with acetylsalicylic acid, with other non-steroidal anti-inflammatory drugs and with platelet aggregate inhibitors (see sections 4.3 and 4.4).

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulants: NSAIDs, including piroxicam, may enhance the effects of anticoagulants, such as warfarin. Therefore, the use of piroxicam with anticoagulants such as warfarin should be avoided (see section 4.3).

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Diuretics, ACE-inhibitors, angiotensin II antagonists and beta-blockers: NSAIDs may reduce the efficacy of diuretics and other anti-hypertensive drugs, most likely by blocking prostaglandin synthesis. In some patients with impaired renal function (e.g. dehydrated patients or elderly patients with impaired renal function), the co-administration of an ACE-inhibitor or an angiotensin II antagonist and agents that inhibit the cyclo-oxygenase system, may further deteriorate renal function, with possible acute renal failure, which is generally reversible. These interactions should be taken into consideration in patients taking piroxicam together with ACE-inhibitors or angiotensin II antagonists.
The combination should therefore be administered with caution, especially in elderly patients.
Patients should be adequately hydrated and renal function monitoring should be considered after starting concomitant therapy.
In case of concomitant intake of potassium-containing drugs, or diuretics that cause potassium retention, there is an additional risk of a rise in serum potassium concentration (hyperkalaemia).

Lithium: The concomitant administration of lithium and NSAIDs, causes an increase in plasma lithium levels; therefore these levels should be monitored at the beginning, during and after the end of treatment with piroxicam.

Methotrexate: when methotrexate is administered together with NSAIDs, including piroxicam, NSAIDs can reduce the elimination of methotrexate and cause an increase in the plasma levels of the latter. Caution is recommended, in particular in patients who take high dosages of methotrexate.

Piroxicam is highly protein bound and therefore displacement of other protein bound drugs is likely. Patients receiving piroxicam with other highly protein bound drugs must be closely monitored by the doctor, in order to adjust dosage if necessary. Piroxicam absorption was slightly increased after cimetidine administration. However, this increase did not prove to be clinically significant.

Alcohol intake should be avoided.

Piroxicam may reduce the effectiveness of intrauterine devices.

Concomitant use of non-steroidal anti-inflammatory drugs and quinolone drugs is not recommended.

Cyclosporin and tacrolimus: the administration of NSAIDs together with cyclosporin or tacrolimus may increase the risk of nephrotoxicity.

4.6 Fertility, pregnancy and breastfeeding

Piroxicam is contraindicated during ascertained or suspected pregnancy, and during breastfeeding (see section 4.3).

Pregnancy

Inhibition of prostaglandin synthesis can adversely affect pregnancy and/or embryo/foetal development.

Results from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation and gastroschisis after the use of a prostaglandin synthesis inhibitor during early pregnancy. The absolute risk of cardiac malformations increased from less than 1% up to approximately 1.5%. It was considered that the risk is dose-related and also increases with duration of therapy.

Animal studies have shown reproductive toxicity (see section 5.3). In animals, the administration of prostaglandin synthesis inhibitors has been shown to cause an increase in pre- and post-implantation losses and in embryo-foetal mortality. Moreover, an increased incidence of various malformations, including cardiovascular malformation, was reported in animals given prostaglandin synthesis inhibitors during organogenesis.

From Week 20 onwards of pregnancy, the use of NSAIDs can cause oligohydramnios arising from fetal renal dysfunction. This condition may be found shortly after the start of treatment and is generally reversible with treatment interruption. Cases of closure of the ductus arteriosus following treatment in the second trimester have also been reported, the majority of which resolved after discontinuation of treatment.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors can expose the foetus to:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, (see above)
Both mother and newborn child, at the end of pregnancy to:
- possible prolongation of bleeding time and anti-aggregating effect that can even occur at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

As a consequence, BREXIN is contraindicated during pregnancy (see sections 4.3 and 5.3).
Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs, including Brexin, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Breastfeeding
Data show that the piroxicam concentration in breast milk lies between 1% and 3% of maternal plasma concentration. Piroxicam is contraindicated during breastfeeding because safety in newborns has not yet been established (see section 4.3).

Fertility
The use of piroxicam could compromise female fertility and it is not recommended in women who are trying to conceive. In women with difficulty conceiving or who are undergoing fertility investigations, treatment with piroxicam should be considered.

4.7 Effects on ability to drive and use machines

Piroxicam can alter the state of alertness to the extent of compromising the ability to drive vehicles or perform activities requiring quick reflexes.

4.8 Undesirable effects

Oedema, hypertension and heart failure have been reported in association with NSAID treatment.

Clinical studies and epidemiological data suggest that the use of some NSAIDs (especially at high doses and for long-term treatments) may be associated with a moderate increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) (see section 4.4).

As for other substances with a similar action, some patients showed increases in

blood urea nitrogen that do not exceed a certain level with prolonged treatment; once therapy is discontinued the values return to baseline.

Undesirable effects are listed in the table below according to the MedDRA System Organ Class, defined using the following convention: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (the frequency cannot be defined based on the available data).

Classification according to MedDRA System Organ Class	**Adverse Reaction**	**Frequency**
Hemolymphopoietic system diseases	Anaemia	Common
	Aplastic anaemia, hemolitic anaemia, thrombocytopenia, leucopenia, eosinophilia, pancytopenia	Rare
Immune system disorders	Serum disease, anaphylaxis, allergic oedema (of face and hands)	Rare
	Hypersensitivity	Not known
Metabolism and nutrition disorders	Fluid retention, hypoglycaemia, hyperglycaemia, abnormal weight gain, loss of appetite, anorexia	Not known
Psychiatric disorders	Depression, strange dreams, hallucinations, insomnia, confusion, mood swings, nervousness, erethism	Not known
Nervous system diseases	Headache	Common
	Dizziness, drowsiness	Uncommon
Eye disorders	Blurred vision	Uncommon
	Sight impairment	Rare
	Vertigo, tinnitus	Common

Ear and labyrinth disorders	Ear impairment	Not known
Vascular disorders	Vasculitis, shock (warning symptoms)	Not known
	Stroke, hypertension	Not known
	Henoch-Schonlein purpura	Rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm, epistaxis	Not known
Gastrointestinal disorders	Abdominal distress, abdominal pain, constipation, diarrhoea, epigastric pain or distress, flatulence, nausea, vomiting, dyspepsia	Common
	Ulcerative stomatitis	Uncommon
	Gastritis, gastrointestinal bleeding, gastrointestinal perforation, melaena, haematemesis, peptic ulcer pancreatitis, dry mouth	Not known
	Exacerbation of colitis*, Crohn's disease*	Not known
Hepatobiliary disorders	Jaundice (rare cases of fatal hepatitis)	Rare
	Hepatitis	Not known
Skin and subcutaneous tissue disorders	Skin rash, pruritus	Common
	Photosensitivity reaction, urticaria, angioedema, non-thrombocytopenic purpura,	Rare
	Severe cutaneous adverse reactions	Very rare

	(SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see section 4.4)	
	Alopecia, skin desquamation, erythema multiforme, ecchymosis, sweating, abnormal nail growth	Not known
	Fixed drug eruption (see section 4.4)	Not known
Renal and urinary disorders	Interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal failure	Rare
	Vesicular dysfunction	Very rare
	Haematuria, dysuria	Not known
	Acute renal failure	Not known
Systemic disorders and administration site conditions	Oedema	Rare
	Malaise, asthenia	Not known
Cardiac disorders	Myocardial infarction, heart failure	Not known
Reproductive system and breast disorders	Female infertility	Not known
Diagnostic tests	Increased liver function tests	Rare
	Increased transaminase levels, weight gain, positive antinuclear antibody, abnormal haematology test, decreased haemoglobin, decreased haematocrit	Not known

* see section 4.4

The most commonly observed adverse events are gastrointestinal. Peptic ulcers, gastrointestinal perforation or bleeding, may occur, and are sometimes fatal, especially in the elderly (see section 4.4).

BREXIN has the prerequisites for being better tolerated than plain piroxicam in the gastrointestinal tract; in fact, the shorter persistence of the active substance in the gastrointestinal tract reduces the risk of contact irritation.

Piroxicam therapy should be discontinued if clinical signs and symptoms of hepatic disturbances occur.
Some cases of acute renal failure, water retention, which can occur as oedema especially in the peripheral regions of the lower limbs or as cardiovascular disorders (hypertension, decompensation) have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms: the most indicative overdose symptoms are headache, vomiting, drowsiness, dizziness and fainting.
In the event of overdose, supportive and symptomatic therapy is indicated.
Although no studies have been performed so far, haemodialysis is not likely to be useful in helping to eliminate piroxicam, as the drug is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory/anti-rheumatic drugs. ATC code: M01AC01.

Mechanism of action
Piroxicam, belonging to the class of benzothiazine-based N-heterocyclic carboxyamides, is the first compound of a new class of NSAIDs, the oxicams. Piroxicam has an anti-inflammatory, analgesic and antipyretic activity, pharmacological actions similar to those of other non-steroidal anti-inflammatory drugs.

Pharmacodynamic effects
Animal studies have shown that piroxicam affects cell migration to sites of inflammation. Like other NSAIDs, piroxicam interferes with prostaglandin synthesis by inhibiting cyclo-oxygenase.

Unlike indomethacin, piroxicam is a reversible inhibitor of prostaglandin synthesis. In a study performed in 9 patients with active rheumatoid arthritis, piroxicam (20 mg/day for 15 days), the function of polymorphonuclear (PMN) cells, the production of superoxide anions in peripheral blood and in synovial fluid and the concentration of PMN and PMN-elastase in synovial fluid were shown to be markedly lowered. Modulation of PMN response may contribute to the anti-inflammatory action of piroxicam.
BREXIN is a new formulation of piroxicam where the active compound is complexed with ß-cyclodextrin.
ß-cyclodextrin is a cyclic oligosaccharide derived from enzymatic hydrolysis of common starch. Due to its particular chemical structure, ß-cyclodextrin can form inclusion complexes ('molecular encapsulation') with various drugs thereby improving their solubility, stability and bioavailability.
Piroxicam-ß-cyclodextrin was found to be very soluble in water and more rapidly absorbed than piroxicam after oral administration.
The improved solubility results in a rapid increase in plasma levels of piroxicam and means the peak value is reached sooner, which is clinically manifested with a quicker onset and greater intensity of the analgesic and anti-inflammatory effect.
As regards piroxicam, the extended plasma half-life of BREXIN is unchanged, thus allowing a once-a-day administration of the product.
The pharmacodynamic and pharmacokinetic properties of BREXIN make it suitable for the treatment of markedly painful rheumatic and/or inflammatory diseases, which seriously compromise the patient's general condition and normal activity, and where it is necessary to obtain a rapid and intense therapeutic effect.

Efficacy and clinical safety
In the carrageenan-induced footpad oedema test, BREXIN produced an anti-inflammatory activity more quickly than piroxicam; in the first hours after administration, in fact, BREXIN was 2-3 times more active than piroxicam by oral route.
The analgesic activity was assessed in mice with the phenylquinone-induced writhing test by oral route; 5 minutes after treatment, 99% of the maximum inhibitory effect was obtained with BREXIN and 78% was obtained with piroxicam. The activity of both drugs remained constant for two hours after administration.
Therapeutic index values for BREXIN and piroxicam were calculated by comparing the anti-inflammatory effects, evaluated in rats with the carrageenan-induced footpad oedema test, with the gastro-irritant effects in the same animal species.
BREXIN by oral route had a therapeutic index 2.65 times higher than oral piroxicam.
The improved gastrointestinal tolerability of BREXIN was confirmed in humans by means of three double-blind controlled studies, in which the presence of blood in the faeces was assessed using the ^{51}Cr-labelled red-cell method. In all these studies, the treatment duration was 28 days. Two studies showed a significantly lower faecal blood loss with BREXIN towards the end of the 4-week study period, while in the third study a similar trend was seen.
In a further study, a comparison was made of the gastric tolerability of BREXIN, piroxicam, indomethacin and placebo after administration over a 14-day period;

the gastric potential difference was also assessed (max GPD). BREXIN produced lesser effects on this parameter than piroxicam or indomethacin, with a positive correlation between the max GPD and endoscopic results.
Therefore, BREXIN shows a more favourable ratio between pharmacodynamic activity and gastrotoxicity than piroxicam.

5.2 Pharmacokinetic properties

Absorption

After oral administration of BREXIN, only the active substance (piroxicam) is absorbed into the circulation, and not the complex as such.
Studies in healthy volunteers demonstrated that, at equivalent doses of piroxicam (20 mg), the piroxicam plasma peak is reached much earlier with BREXIN (within 30-60 minutes, compared to an average of 2 hours with plain piroxicam by the oral route).

Biotransformation

ß-cyclodextrin is metabolized in the colon by bacterial microflora into linear dextrin, maltose and glucose.

Distribution and elimination

The elimination parameters, Kel and half-life, do not differ from those of piroxicam, as complexation with ß-cyclodextrin affects only absorption kinetics and not elimination kinetics.
Urinary excretion of the active substance over 72 hours, for BREXIN and for plain piroxicam, is about 10% of the administered dose.
After oral administration of the complex, no ß-cyclodextrin was detected in plasma or urine.

5.3 Preclinical safety data

Non-clinical data show that there are no particular risks to humans, on the basis of conventional studies on pharmacological safety, repeated dose toxicity, genotoxicity, carcinogenic potential and reproduction toxicity.
As for other prostaglandin synthesis inhibitors, also piroxicam increases the incidence of dystocia and post-term deliveries in animals when the drug is administered throughout pregnancy. Administration of NSAIDs to pregnant rats may cause constriction of the foetal ductus arteriosus. Moreover, in the last trimester of pregnancy, gastro-duodenal toxicity is increased.

Non-clinical studies showed some effects such as gastrointestinal lesions and renal papillary necrosis, at the highest dose used, which was about 60 times higher than the suitable dose for humans.

Such exposure to piroxicam is therefore considered sufficiently in excess of the maximum human exposure, indicating little relevance of these effects for the clinical use of the drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, crospovidone, sodium carboxymethyl starch, colloidal anhydrous silica, modified starch, magnesium stearate.

6.2 Incompatibilities

Not known.

6.3 Expiry date

The expiry date of the product is indicated on the packaging materials. The shelf-life period mentioned above refers to the product correctly stored in its unopened package.

6.4. Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC laminate blisters, sealed with Al/PVDC.
Pale yellow, hexagonal tablets with deep median score.

Box of 4, 10, 20 or 30 tablets 20 mg

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and handling

Any unused product or waste material deriving from it should be disposed of in accordance with local requirements.

7. MANUFACTURER

Chiesi Farmaceutici S.p.A., Parma, Italy

8. MARKETING AUTHORIZATION HOLDER

Taro International Ltd – 14 Hakitor st., Haifa Bay 2624761

9. MARKETING AUTHORIZATION NUMBER

136-61-29695-00

Updated in September 2023 according to MoH instructions.