SUMMARY OF PRODUCT CHARACTERISTICS

BREXIN

1. Name of the Medicinal Product
   BREXIN 20 mg TABLETS
   BREXIN 20 mg POWDER FOR ORAL SOLUTION (SACHETS)

2. Qualitative and Quantitative Composition
   Each tablet contains 20 mg piroxicam (as Beta-Cyclodextrin)
   For excipients see section 6.1

   Each sachet contains 20 mg piroxicam (as Beta-Cyclodextrin)
   For excipients see section 6.1

3. Pharmaceutical Form
   Tablet
   Pale yellow, hexagonal tablet with a median score line on one side

   Sachet
   White or slightly yellow crystalline powder.

4. Clinical Particulars

4.1 Therapeutic Indications
   Piroxicam is indicated for symptomatic relief of osteoarthritis, rheumatoid arthritis or
   ankylosing spondylitis.

   Due to its safety profile (see sections 4.2, 4.3 and 4.4), piroxicam is not a first line
   option should an NSAID be indicated. The decision to prescribe piroxicam should be
   based on an assessment of the individual patient’s overall risks (see sections 4.3 and
   4.4).

4.2 Posology and Method of Administration
   Route of Administration (for oral use)
   Tablets
   Two equivalent halves of a tablet (10 mg as piroxicam), are obtained by placing the
   tablet on a hard surface, with the score fracture line upwards and pressing it in half
   using the thumb.

   Sachets
   The sachet is divided in the middle in a way that allows you to use exactly the half
   dose.
In accordance with the doctor’s instructions, the contents of the sachet or half of its contents should be dissolved in a half glass of water. Stir until dissolved and drink immediately.

**Dosage Recommendations**

*Adults*

The prescription of piroxicam should be initiated by physicians with experience in the diagnostic evaluation and treatment of patients with inflammatory or degenerative rheumatic diseases.

The maximum recommended daily dose is 20 mg, administered as one single daily dose, preferably with or after food. Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.4). The benefit and tolerability of treatment should be reviewed within 14 days. If continued treatment is considered necessary, this should be accompanied by frequent review.

Given that piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

*Children*

The use of piroxicam in children is not recommended.

*The Elderly*

In elderly patients, it may be necessary to reduce the dosage (half a tablet/sachet), and limit the duration of treatment. Again, it is preferable to take the dose with or after food.

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events.

**4.3 Contra-indications**

- known hypersensitivity to any of the constituents or piroxicam
- history of gastro-intestinal ulceration, bleeding or perforation
- patient history of gastrointestinal disorders that predispose to bleeding disorders such as ulcerative colitis, Crohn’s disease, gastrointestinal cancers or diverticulitis
- patients with active peptic ulcer, inflammatory gastrointestinal disorder or gastrointestinal bleeding
- concomitant use with other NSAIDs, including COX-2 selective NSAIDs and acetylsalicylic acid at analgesic doses
- concomitant use with anticoagulants
- history of previous serious allergic drug reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- hypersensitivity to the active substance, previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications
- porphyria
- severe heart failure

Brexin is contra-indicated in children.

4.4 Special Warnings and Precautions for Use
Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2).
The clinical benefit and tolerability should be re-evaluated periodically and treatment should be immediately discontinued at the first appearance of cutaneous reactions or relevant gastrointestinal events.

**Gastrointestinal (GI) Effects, Risk of GI Ulceration, Bleeding and Perforation**
NSAIDs, including piroxicam, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.
NSAID exposures of both short and long duration have an increased risk of serious GI event. Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs.
Patients with significant risk factors for serious GI events should be treated with piroxicam only after careful consideration (see sections 4.3 and below).
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).

**Serious GI Complications**
Identification of at-risk subjects
The risk of developing serious GI complications increases with age. Age over 70 years is associated with high risk of complications. The administration to patients older than 80 years should be avoided.
Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as low-dose acetylsalicylic acid are at increased risk of serious GI complications (see below and section 4.5). As with other NSAIDs, the use of piroxicam in combination with protective agents (e.g. misoprostol or proton pump inhibitors) must be considered for these at-risk patients.
Patients and physicians should remain alerted for signs and symptoms of GI ulceration and/or bleeding during piroxicam treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately and additional clinical evaluation and treatment should be considered.
Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient 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 only be treated with piroxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

To avoid the risk of increased side effects, piroxicam should not be given with other non-steroidal anti-inflammatory agents.

In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function in such patients, should occur prior to the initiation of therapy and regularly thereafter.

Piroxicam may cause a decrease in platelet aggregation and prolongation of bleeding time. This effect should be kept in mind when bleeding times are determined.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Caution is required if piroxicam is administered to patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

There are reports of reversible elevation of blood urea, nitrogen and creatinine.

In rare cases, NSAIDs may cause interstitial nephritis, glomerulitis papillary necrosis and nephrotic syndrome. They inhibit synthesis of renal prostaglandin that plays a supportive role in maintaining renal perfusion in patients with reduced blood volume and renal blood flow. In such patients, administration of a NSAID may precipitate overt renal decompensation, which is followed by recovery to the pre-treatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome or overt renal disease. Such patients should be monitored carefully whilst receiving NSAID therapy.
Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Evidence from observational studies suggests that piroxicam may be associated with a higher risk of serious skin reactions than other non-oxicam NSAIDs. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other signs of hypersensitivity.

4.5 Interactions with Other Medicaments and Other Forms of Interaction
Care should be taken in patients treated with any of the drugs mentioned below because, as with other NSAIDs, piroxicam has the potential to induce the following interactions.

Other Analgesics
As with other NSAIDs, the use of piroxicam together with acetylsalicylic acid or concomitant use with 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 enhanced (see section 4.4). Human studies have shown that concomitant use of piroxicam and acetylsalicylic acid reduces the plasma piroxicam concentration to about 80% of the usual value.

Anti-hypertensives
There may be a reduction in the effect of anti-hypertensives.

Diuretics
Piroxicam may cause sodium, potassium and fluid retention, and may interfere with the natriuretic action of diuretic drugs causing a reduction in the diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension, to avoid a possible worsening of these conditions.

Cardiac Glycosides
NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycosides levels.

Concomitant administration of antacids had no effect on piroxicam plasma levels, nor did concurrent therapy of piroxicam with digoxin or digitoxin affect the plasma levels of either drug.
Sulphonamides and Hydantoins
Piroxicam is highly protein bound, and therefore, it might be expected to displace other protein bound drugs e.g. anticoagulants, sulphonamides and hydantoins such as phenytoin. Patients must be monitored closely for change in dosage requirements when giving Brexin to patients already receiving other highly protein bound drugs.

Anticoagulants
NSAIDs, including piroxicam, may enhance the effects of anti-coagulants, such as warfarin. Therefore, the use of piroxicam with concomitant anticoagulant such as warfarin should be avoided (see section 4.3). Brexin.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)
Increased risk of gastrointestinal bleeding (see section 4.4).

Cimetidine
There is some evidence that a slight but significant increase in absorption of piroxicam may occur following administration of cimetidine - with no significant changes in elimination rate constants or half-life. It is unlikely that this small increase in absorption is of clinical significance.

Lithium
NSAIDs, including piroxicam, have been reported to decrease the elimination of lithium. It is recommended that the levels of lithium are monitored when initiating, adjusting or discontinuing treatment with piroxicam.

Quinolone Antibiotics
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Mifepristone
In common with other NSAIDs, piroxicam should be avoided for at least 8 to 12 days following mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Methotrexate
There is decreased elimination of methotrexate with NSAIDs.

Ciclosporin
NSAIDs may increase ciclosporin nephrotoxicity as a result of their effect on renal prostaglandins.

Corticosteroids
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Aminoglycosides
Reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations have been reported.

Probenecid
Reduction in metabolism and elimination of NSAID and metabolites occurs with probenecid.

Oral Hypoglycaemic Agents
Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia is known to occur with oral hypoglycaemic agents.

4.6 Pregnancy and Lactation
Although no teratogenic effects have been demonstrated in animal toxicology studies, the use of NSAIDs during pregnancy should, if possible, be avoided. Congenital abnormalities have been reported in association with NSAID administration in man. However, these are low in frequency and do not appear to follow any discernible pattern.

Piroxicam inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme. This effect, as with other NSAID, is associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued into late pregnancy. NSAIDs are also known to induce closure of the ductus arteriosus in infants and therefore, use in late pregnancy should be avoided.

A study indicates that piroxicam is found in breast milk at about 1% to 3% of the maternal plasma concentrations. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment for up to 52 days. Brexin is not recommended for use in nursing mothers because clinical safety in neonates has not been established.

4.7 Effects on Ability to Drive and Use Machines
Piroxicam can alter the state of alertness to such an extent that driving vehicles or performing activities which require quick reflexes (such as operating machinery), may be affected.

Since swollen eyes, blurred vision and eye irritation have been reported in association with the use of piroxicam, and dizziness, drowsiness or headaches are possible side effects associated with taking NSAIDs, patients should be warned to take care when undertaking such activities.

Although routine ophthalmology and slit-lamp examinations have not shown evidence of ocular changes such examinations should be performed if these symptoms develop.
4.8 Undesirable Effects

Gastrointestinal
Gastrointestinal symptoms associated with piroxicam administration are the most common side effects, but in most cases do not interfere with continuation of therapy. These include ulcerative stomatitis, anorexia, epigastric or abdominal discomfort or pain, nausea, constipation, flatulence, diarrhoea and indigestion, vomiting, dyspepsia, melaena and haematemesis.

Gastric ulceration, duodenal ulcer and gastrointestinal perforation and gastrointestinal bleeding, in rare cases fatal, have been reported with piroxicam. Long-term administration of piroxicam in a dose of 30 mg per day or more carries an increased risk of gastrointestinal side effects.

Hypersensitivity Reactions
There are rare reports of piroxicam causing cutaneous hypersensitivity reactions such as rash or pruritus, urticaria, angioedema, onycholysis or alopecia. As with other NSAIDs, epidermal necrolysis (Lyell’s disease), Stevens-Johnson syndrome or vesiculo-bullous reactions may occur rarely.

These reactions may also consist of respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea.

There may be other non-specific allergic reactions and anaphylaxis.

Other hypersensitivity reactions such as vasculitis and serum sickness have been rarely reported.

Dermatological Reaction
Photosensitivity reactions occur infrequently.

Renal
Rarely, NSAIDs may cause interstitial nephritis, glomerulo-nephritis, nephrotic syndrome and renal failure.

Haematological Reactions
Decreases in haemoglobin and haematocrit in the absence of obvious gastrointestinal bleeding have occurred and anaemia has been reported, as have thrombocytopenia, non-thrombocytopenic purpura (Henoch-Schoenlein), leucopenia and eosinophilia. There are rare reports of aplastic anaemia, haemolytic anaemia and epistaxis.

Hepatic
Changes in various liver function parameters have been seen with piroxicam and, as with other NSAIDs, some patients may show an increase in serum transaminase concentration during piroxicam treatment; also, severe hepatic reactions, including jaundice and cases of fatal hepatitis have also occurred.
Even though such events are rare, where abnormal liver function tests persist or worsen or clinical signs consistent with liver disease develop, or there are systemic manifestations (such as a rash or eosinophilia), treatment should be discontinued.

**Cardiovascular**
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Equally, elderly, frail or debilitated patients require careful supervision because they may tolerate side effects less well; the elderly require caution since they are more likely to have impaired renal, hepatic or cardiac function.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

**Neurological and Special Senses**
CNS effects including dizziness, headache, somnolence, insomnia, depression, nervousness, hallucinations, mood alterations, dream abnormalities, mental confusion, paraesthesias, vertigo, visual disturbances, optic neuritis, tinnitus, malaise, fatigue and drowsiness have all been reported.

Palpitations, metabolic abnormalities such as hypoglycaemia, weight increase or decrease and anecdotal cases of positive ANA or hearing impairment have all been reported.

### 4.9 Overdose
**Symptoms**
The most likely symptoms of overdose are headache, vomiting, drowsiness, dizziness and fainting.

**Management**
In the event of an overdose with Brexin, supportive and symptomatic management is necessary and may include gastric lavage and the use of oral activated charcoal to reduce absorption of piroxicam. The correction of severe electrolyte abnormalities may need to be considered.

5. **Pharmacological Properties**

5.1 **Pharmacodynamic Properties**
Brexin is an inclusion complex of piroxicam and βeta-cyclodextrin (piroxicam βetadex). It is a non-steroidal anti-inflammatory drug.

The faster dissolution characteristics of piroxicam βetadex (about 100 % in 10 minutes) with respect to piroxicam alone, results in a quicker absorption of the active
ingredient and promotes a more rapid onset of analgesic action (see Pharmacokinetics).

5.2 Pharmacokinetic Properties
As a NSAID, piroxicam is well absorbed after oral administration and is extensively metabolised by the liver with elimination occurring via the kidneys.

The drug has a plasma half-life of about 50 hours with the maintenance of plasma levels for up to 24 hours. Steady state levels are reached in 7 to 12 days and maintained with little change for up to a year of treatment.

The absorption of piroxicam from piroxicam βetadex is more rapid than that of piroxicam alone, so that the time taken to reach the maximum plasma concentration ($T_{max}$), is much shorter; clinically this is reflected by a more rapid onset of acute analgesia after single doses.

Studies on healthy volunteers demonstrated that, after single oral administration at equivalent doses (20 mg as piroxicam), piroxicam from piroxicam βetadex was absorbed at least 2 times faster than it was as the plain drug. The maximum plasma concentration ($C_{max}$) of piroxicam was reached within 30 to 60 minutes with piroxicam βetadex and was higher than that obtained after 2 hours with plain piroxicam.

5.3 Preclinical Safety Data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicology and toxicology of reproduction.

6. Pharmaceutical Particulars

6.1 List of Excipients
Tablet
Lactose monohydrate, crospovidone, sodium starch glycollate, colloidal silicon dioxide, pregelatinised starch, magnesium stearate

Sachet
Sorbitol, citrus flavor, aspartame, silica, colloidal anhydrous.
Each sachet contains 8.4 mg phenylalanine.

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
36 months

6.4 Special Precautions for Storage
No special precautions for storage
6.5 **Nature and Contents of Container**

**Tablets**
The tablets are enclosed in opaque blisters composed of 250 µm PVC coated with 40 g m$^{-2}$ PVDC and 25 µm aluminium coated with 18 to 20 g m$^{-2}$ PVDC.

The blisters are boxed in cardboard cartons containing 20 tablets and a user leaflet.

**Powder for oral solution**
Double-sheet paper / aluminum / polyethylene sachets

The sachets are boxed in cardboard cartons containing 10 sachets and user leaflet.

6.6 **Instruction for Use / Handling**
Not applicable

7. **Manufacturer**
Chiesi Farmaceutici S.p.A.,
Parma, Italy

8. **License Holder**
Taro International Ltd.,
14 Hakitor Street, Haifa Bay, Israel