SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Adex® 200 / Ibupro 200
Adex® forte 400 / Ibupro forte 400 / Ibufen® 400
Adex® liqui-gels 200 / Ibupro liqui-gels 200
Adex® liqui-gels 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Adex 200 / Ibupro 200 / Adex liqui-gels 200 / Ibupro liqui-gels 200 contain 200 mg Ibuprofen
Adex forte 400 / **Ibupro forte 400 / Ibufen 400 / Adex liqui-gels 400:** contain 400 mg Ibuprofen
Each capsule of **Adex liqui-gels 200 / Ibupro liqui-gels 200** contains approximately 7mg of sorbitol.
Each capsule of **Adex liqui-gels 400** contains approximately 11mg of sorbitol.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Adex 200 / Ibupro 200: Pink, film-coated, caplets, scored on one side.
The caplet can be divided into equal doses.

Adex forte 400 / Ibupro forte 400 / Ibufen 400: White, film-coated, caplets, scored on both sides.
The caplet can be divided into equal doses.

Adex liqui-gels 200 / Ibupro liqui-gels 200: Blue, soft gelatine capsules imprinted with "200".
Adex liqui-gels 400: Blue, soft gelatine capsules imprinted with "400".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adex 200 / Ibupro 200 / Adex forte 400 / Ibupro forte 400 / Ibufen 400:
For the treatment of pain associated with migraine.
For the relief of mild to moderate pain such as headache, toothache, primary dysmenorrhea, backache, muscular pain.
Anti - inflammatory and relieves pain in rheumatoid arthritis and osteoarthritis.
Adex 200 / Ibupro 200 are also indicated for the reduction of fever.

Adex liqui-gels 200/ Adex liqui-gels 400/ Ibupro liqui-gels 200:
For the treatment of pain associated with migraine.
Relief of mild to moderate pain such as headache, toothache, menstrual pain, backache, muscular pain, anti-inflammatory for rheumatic disease. Reduction of fever.

4.2 Posology and method of administration

For oral administration and short-term use only.
During short-term use, if symptoms persist or worsen the patient should be advised to consult a doctor.

Adults and children and adolescents between 12 and 18 years:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
If in adults the product is required for more than 10 days, or if the symptoms worsen the patient should consult a doctor.
If in children and adolescents between 12 and 18 years this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Adults, Children and Adolescents between 12 and 18 years:

Take 200mg or 400mg with water, up to three times a day as required.

Leave at least four hours between doses.

Do not take more than 1200 mg in any 24 hour period.

Not for use by children under 12 years of age.

4.3 Contraindications

- Hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1.
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to aspirin or other non-steroidal anti-inflammatory drugs.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. (See Section 4.4).
- Severe heart failure (NYHA Class IV), renal failure or hepatic failure (see section 4.4)
- Last trimester of pregnancy (See section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory:
Bronchospasm may be precipitated in patients suffering from, or with a previous history of, bronchial asthma or allergic disease.

Other NSAIDs:
The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

SLE and mixed connective tissue disease:
Systemic lupus erythematosus as well as those with mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8).

Renal:
Renal impairment as renal function may further deteriorate (see sections 4.3 and 4.8).
There is a risk of renal impairment in dehydrated children and adolescents.

Hepatic:
Hepatic dysfunction (see sections 4.3 and 4.8).

Cardiovascular and cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies and epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400mg/day) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility:
There is limited evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Gastrointestinal:

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Dermatological:
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). Patients appear to be at highest risk for 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. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Advice for patients with sugar-related disorders:
Adex liqui-gels 200 / Ibupro liqui-gels 200/ Adex liqui-gels 400 contain Sorbitol.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen (like other NSAIDs) should be avoided in combination with:

Aspirin: unless low-dose aspirin (not above 75mg daily) has been advised by a doctor as this may increase the risk of adverse reactions (see Section 4.4). Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly.
However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).
Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ibuprofen should be used with caution in combination with:

Corticosteroids: as these may increase the risk of gastrointestinal ulceration or bleeding (see Section 4.4).

Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: since NSAIDs may diminish the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal

failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

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

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

Lithium: There is evidence for potential increase in plasma levels of lithium.

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryfoetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

- the foetus to:

  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction, which may progress to renal failure with oligohydroamniosis;
- the mother and the neonate, at the end of the pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Breast-feeding:

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

None expected at recommended dose and duration of therapy.

4.8 Undesirable effects

Adverse events which have been associated with Ibuprofen are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

The list of the following adverse events relates to those experienced with ibuprofen at OTC doses for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent; in particular the risk of occurrence of gastrointestinal bleeding is dependent on the dosage range and duration of treatment.

Clinical trial and epidemiological data suggest that use of ibuprofen, (particularly at a high dose 2400mg/day) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke), (see section 4.4).

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.
Immune System Disorders	Uncommon Very rare	Hypersensitivity reactions consisting of[1]: Urticaria and pruritus Severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension

	Not Known	(anaphylaxis, angioedema or severe shock). Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
Nervous System Disorders	Uncommon Very rare	Headache Aseptic meningitis[2]
Cardiac Disorders	Not Known	Cardiac failure and oedema
Vascular Disorders	Not Known	Hypertension
Gastrointestinal Disorders	Uncommon Rare Very rare Not Known	Abdominal pain, nausea, dyspepsia Diarrhoea, flatulence, constipation and vomiting Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis Exacerbation of colitis and Crohn's disease (section 4.4).
Hepatobiliary Disorders	Very rare	Liver disorders
Skin and Subcutaneous Tissue Disorders	Uncommon Very rare	Various skin rashes Severe forms of skin reactions such as bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis can occur.
Renal and Urinary Disorders	Very rare Not Known	Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema. Renal insufficiency
Investigations	Very rare	Decreased haemoglobin levels

Description of Selected Adverse Reactions

[1]Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm, dyspnoea or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

[2]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or disorientation) have been observed during treatment with ibuprofen, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

In children ingestion of more than 400mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5-3 hours.

Symptoms:

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Management:

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01AE01 Propionic acid derivative.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Clinical evidence demonstrates that when 400mg of ibuprofen is taken the pain relieving effects can last for up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (acetylsalicylic acid) on platelet aggregation when they are dosed concomitantly.

Some pharmacodynamics studies show that when single doses of ibuprofen 400mg were taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of aspirin (acetylsalicylic acid) on the formation of thromboxane or platelet aggregation occurred.

Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract. Ibuprofen is extensively bound to plasma proteins.
The median peak plasma concentration for Ibuprofen tablets is achieved approximately 1-2 hours after administration.
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete.
Elimination half-life is approximately 2 hours.
No significant differences in pharmacokinetic profile are observed in the elderly.

5.3 Preclinical safety data

No relevant information, additional to that contained elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adex 200 / Ibupro 200:

Microcrystalline cellulose, Maize starch, Croscarmellose sodium, Magnesium stearate, Hypromellose, Carmellose sodium, Silica colloidal anhydrous, Talc, Stearic acid, Titanium dioxide E-171, Erythrosine aluminium lake E-127, Macrogol, Carnauba wax, Quinoline yellow aluminium lake E-104, Brilliant blue FCF aluminium lake E-133.

Adex forte 400 / Ibupro forte 400 / Ibufen 400:

Microcrystalline cellulose, Maize starch, Croscarmellose sodium, Magnesium stearate, Carmellose sodium, Silica colloidal anhydrous, Hypromellose, Stearic acid, Titanium dioxide E-171, Talc, Macrogol, Carnauba wax.

Adex liqui-gels 200 / Adex liqui-gels 400 / Ibupro liqui-gels 200:

Macrogol 600, Purified water, Potassium hydroxide, Gelatin, Sorbitol, Sorbitan-1,4, Maize starch, Higher polyols, Mannitol, Patent blue E-131, Titanium dioxide E-171.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Adex 200, Adex forte 400, Ibupro 200, Ibupro forte 400, Ibufen 400: Store in a dry place, not above 25°C.
Adex liqui-gels 200, Adex liqui-gels 400, Ibupro liqui-gels 200: Do not store above 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes:

Adex 200: 10, 16, 20, 30, 40, 50, 100, 1000 caplets

Adex forte 400: 10, 20, 30, 40, 50, 100, 1000 caplets

Ibupro 200: 10, 16, 20, 30, 50, 100, 1000 caplets

Ibupro forte 400 / Ibufen 400: 10, 20, 30, 50, 100, 1000 caplets

Adex liqui-gels 200 / Adex liqui-gels 400 / Ibupro liqui-gels 200: 2, 4, 8, 10, 16, 20, 24, 30, 32, 40, 50, 60, 70, 80 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd.
1 Dexcel Street, Or Akiva, 3060000, Israel

8. MANUFACTURER

Dexcel Ltd.
1 Dexcel Street, Or Akiva, 3060000, Israel

This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in May 2018.