

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac Bluefish 25 mg gastro-resistant tablets
Diclofenac Bluefish 50 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains diclofenac sodium 25 mg or 50 mg respectively.

Excipient with known effect:
Lactose monohydrate 50 mg or 65 mg respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

25 mg gastro-resistant tablets: Domed film-coated yellow tablets, 7 mm in diameter, marked D 25.
50 mg gastro-resistant tablets: Domed film-coated brown tablets, 8 mm in diameter, marked D 50.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special Warnings and precautions for use).

Treatment should begin at the lowest expected effective dose, with subsequent adjustment on the basis of therapeutic response and any side-effects. With long-term treatment, a low maintenance dose should be aimed for.

Rheumatic disorders: Adults 75-150 mg daily divided into 2-3 doses depending on disease activity.

Impaired hepatic or renal function:

No dosage reduction appears to be necessary for patients with mild to moderate hepatic or renal impairment. Diclofenac is contraindicated in patients with severe hepatic or renal impairment (see Section 4.3). Patients with moderate renal or hepatic impairment should be carefully monitored. The lowest effective dose should be given.

Elderly patients:

The aim should be to administer the lowest effective dose (see Section 4.4).

Paediatric population:

Diclofenac Bluefish should not be given to children and adolescents under 18 years of age.

The maximum recommended daily dose is 150 mg.

Method of administration

The tablets are to be swallowed whole with fluid.

For maximum effect, the tablets are not to be taken with or directly after a meal since food may delay the passage through the stomach.

Monitoring of treatment

In the case of long-term treatment with Diclofenac Bluefish, laboratory blood values and liver and kidney function values should be monitored.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Active gastric or intestinal ulcer, bleeding or perforation.
- 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 NSAID therapy.
- Conditions giving an increased tendency to bleeding.
- Severe hepatic-, or renal failure (glomerular filtration < <15 ml/min/1.73 m²) (see section 4.4)
- Hepatic porphyria.
- The third trimester of pregnancy (see section 4.6).

Due to cross-reaction, the medicinal product should not be given to patients, especially asthmatics, who have experienced symptoms of asthma, angioedema, acute rhinitis or urticaria after taking aspirin or other non-steroidal anti-inflammatory agents.

4.4 Special warnings and precautions for use

General

There is a clear correlation between the dose and serious gastrointestinal side effects. Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2 and Gastrointestinal effects and cardiovascular and cerebrovascular effects below).

Concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Elderly patients are also more likely to suffer from impaired renal, heart or liver function. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight (see section 4.2).

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can

also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Patients with gastrointestinal problems or with a previous ulcer as well as patients with ulcerative colitis, Crohn's disease, impaired hepatic function, SLE, haematopoiesis or coagulation disorders should be kept under careful monitoring when treated with diclofenac.

Gastrointestinal effects

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

Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, including diclofenac, at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The consequences are often more serious in the elderly. Treatment should be discontinued in patients who develop gastrointestinal bleeding or ulceration.

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see 4.8). 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. Elderly patients have more frequent side effects due to NSAIDs, especially gastrointestinal bleeding and perforation, some with a fatal outcome.. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose of acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly when 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 acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Diclofenac Bluefish, treatment should be withdrawn.

Hepatic effects

As for other NSAIDs, serious liver damage has been reported during treatment with diclofenac (see section 4.8).

Close medical surveillance is required when prescribing Diclofenac Bluefish to patients with impaired hepatic function, as their condition may be exacerbated. As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac Bluefish, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis

may occur with use of diclofenac without prodromal symptoms.

Treatment with NSAIDs in patients with chronic liver disease should be avoided if possible because of possible increased risk of gastrointestinal bleeding.

Caution is called for when using Diclofenac Bluefish in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac Bluefish in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (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. Diclofenac Bluefish should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Diclofenac Bluefish in case of varicella.

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 diclofenac (particularly at high doses, 150mg daily and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Patients should be alert for signs and symptoms of serious arteriothrombotic events (e.g., chest pain, shortness of breath, weakness, slurred speech) that may occur without warning. Patients should be instructed to seek immediate medical attention if any of these symptoms occur

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treated for more than 4 weeks

Haematologic effects

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Diclofenac Bluefish may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Other

Patients who are being treated with oral anticoagulants or antidiabetics should be monitored with respect to overdose in the event of concomitant treatment with diclofenac. Laboratory tests should be carried out in order to check that the desired effect of anticoagulants is maintained. Isolated cases of hypoglycaemia and of hyperglycaemic effects that require dose adjustment of antidiabetic agents have been reported.

NSAIDs can inhibit the diuretic effect and enhance the potassium-sparing effect of diuretics, which makes it necessary to check serum potassium levels.

As with other analgesics, the following applies: if patients with acute abdominal pain are repeatedly given pain relief, this can modify or disguise the pattern of symptoms of associated complications such as perforation.

Prolonged use of any type of painkiller for headaches can make the headache worse. If this situation is experienced or suspected, treatment should be discontinued. The diagnosis of Medication Overuse Headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Use of diclofenac can reduce fertility and it is for this reason not recommended in women attempting to conceive. This is true for all medicinal products that inhibit the synthesis of cyclooxygenase and prostaglandins. The effect is reversible and ends when the use of these types of medicinal products is discontinued (see section 4.6).

As with other NSAIDs, the pharmacodynamic properties of diclofenac mean that it can mask the signs or symptoms of infection.

Diclofenac Bluefish contains lactose

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

Diclofenac Bluefish contains sodium

Diclofenac Bluefish medicine contains less than 1 mmol sodium (23 mg) per 25mg and 50mg tablets that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interactions

Pharmacodynamic interactions

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in

patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIS): Increased risk of gastrointestinal bleeding (see section 4.4)

Heparin (parenteral administration): An increased risk of bleeding (inhibition of platelet function and increased gastrointestinal side effects of NSAIDs).

Pentoxifylline: Increased risk of bleeding: increased clinical monitoring and check of bleeding times are recommended.

Zidovudine: Increased risk of bleeding (haemarthrosis and haematoma) in HIV-positive haemophilic patients.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

Medicinal products causing hyperkalaemia: Concomitant treatment with potassium-sparing medicinal products (such as potassium-sparing diuretics), ciclosporin, tacrolimus or trimethoprim may lead to increased serum potassium concentration, which should therefore be monitored regularly (see section 4.4).

Angiotensin II antagonists: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. 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.

Other NSAIDs: Concomitant systemic administration of other NSAIDs should in general be avoided due to the increased risk of gastrointestinal adverse events (see section 4.4).

Quinolones: Convulsions may occur as a consequence of interactions between quinolones and NSAIDs. They can occur in patients with or without a previous history of epilepsy or convulsions. For this reason, care should be taken when considering the administration of quinolones to patients already taking NSAIDs.

Oral antidiabetics: Clinical trials have shown that diclofenac does not influence the effect of antidiabetic agents, although there have been isolated reports of hypoglycaemia and hyperglycaemia that have required dose adjustment of the antidiabetic during diclofenac treatment. Therefore, blood glucose monitoring is recommended as a precautionary measure during concomitant treatment.

Corticosteroids: Concomitant treatment with diclofenac and corticosteroids can increase the risk of gastrointestinal bleeding (see section 4.4).

Pharmacokinetic interactions

Effects of diclofenac on the pharmacokinetics of other drugs:

Methotrexate: NSAIDs inhibit the tubular secretion of methotrexate, leading to increased plasma concentrations. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentration of methotrexate may rise, and the toxicity of this substance be increased. High-dose treatment with methotrexate should be avoided with concomitant diclofenac treatment. Care should be observed during concomitant low-dose treatment and patients should be monitored with respect to methotrexate-related toxicity.

Lithium: Diclofenac reduces the renal clearance of lithium by about 20% and thus increases serum lithium levels. It may be necessary to adjust the lithium dose. The combination should be avoided unless frequent checks of serum lithium can be carried out at the time of the introduction and the discontinuation of the treatment.

Cyclosporin and tacrolimus: A relatively high frequency of nephrotoxicity (increasing levels of serum creatinine) with increasing blood pressure has been observed during concomitant treatment with diclofenac and cyclosporine (for rheumatoid arthritis). It is probable that the risk is present during concomitant treatment with tacrolimus. Furthermore, the plasma concentration of diclofenac doubled following a single oral dose of cyclosporine during ongoing diclofenac treatment. Combination treatment should be carried out with care. The dose of diclofenac should be halved if combination treatment is given.

Digoxin: Trials in healthy subjects show that the introduction of diclofenac in persons being treated with digoxin results in increased plasma levels of digoxin. Plasma digoxin levels should be monitored when instituting diclofenac and when discontinuing treatment, since adjustment of the dose may be necessary.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Effects of other drugs on the pharmacokinetics of diclofenac:

Drugs that inhibit or induce the enzyme CYP2C9: The metabolism of diclofenac is catalysed by the enzyme CYP2C9. Concomitant treatment with drugs (such as fluconazole) that inhibit this enzyme probably lead to higher concentrations of diclofenac in plasma. Drugs such as rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, and barbiturates, which induce CYP2C9 activity, can reduce the plasma concentration of diclofenac to subtherapeutic levels. Diazepam, which is metabolised via CYP2C19, increases the plasma concentration of diclofenac by 50–100%.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as fluconazole, amiodarone, sulfapyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism. Co-administration of voriconazole resulted in 78% and 114% increases in AUC and C_{max} , respectively, for diclofenac.

Colestipol and cholestyramine: Concomitant administration of diclofenac with colestipol or cholestyramine delays the absorption or reduces the absorption of diclofenac by about 30% (colestipol) and 60% (cholestyramine). Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

The rate of absorption of diclofenac is reduced when Diclofenac Bluefish is taken with meals. It is therefore not advisable for the tablets to be taken with or immediately after meals.

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 embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, Diclofenac Bluefish use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Diclofenac Bluefish should not be given unless clearly necessary. If Diclofenac Bluefish 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Diclofenac Bluefish for several days from gestational week 20 onward. Diclofenac Bluefish should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above): which may progress to renal failure with oligo-hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Diclofenac Bluefish is contraindicated during the third trimester of pregnancy (see 4.3 and 4.4).

Breastfeeding

Like other NSAID, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of Diclofenac Bluefish may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac Bluefish should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Gastrointestinal problems can occur at the start of treatment in approximately 10% of patients. These undesirable effects normally disappear after a few days, even if treatment is continued.

Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Such problems can occur at any time during treatment, with or without warning symptoms and with or without previous history of disease.

Diclofenac temporarily inhibits platelet aggregation, which may lead to increased risks in patients with various bleeding conditions.

The following frequencies are used for the description of the occurrence of adverse reactions:

Very common ($>1/10$), Common ($>1/100$, $<1/10$), Uncommon ($>1/1000$, $<1/100$), Rare ($>1/10,000$, $<1/1000$), Very rare ($<1/10,000$), Not known (frequency cannot be estimated from the available data).

The following undesirable effects include those reported with either short-term or long-term use.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, agranulocytosis, anaemia (including haemolytic- and aplastic anaemia).

Immune system disorders

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioneurotic oedema (including face oedema).

Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, anxiety, psychotic disorder.

Nervous system disorders

Common: Headache, dizziness.

Rare: Somnolence.

Very rare: Paraesthesia, memory impairment, convulsions, tremor, taste disturbances, aseptic meningitis, cerebrovascular accident.

Eye disorders

Very rare: Visual disturbance, vision blurred, diplopia.

Ear and labyrinth disorders

Common: Vertigo

Very rare: Tinnitus, hearing impaired.

Cardiac disorders

Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

Not known: Kounis syndrome

Vascular disorders

Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm.

Rare: Asthma (including dyspnoea).

Very rare: Pneumonitis.

Gastrointestinal disorders

Common: Epigastric pain, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, flatulence, anorexia.

Rare: Gastritis, gastrointestinal bleeding, haematemesis, melena, gastrointestinal ulcer (with or without bleeding or perforation), haemorrhagic diarrhoea.

Very rare: diaphragm-like intestinal strictures, colitis (including haemorrhagic colitis and exacerbation of ulcerous colitis or Crohn's disease), stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, constipation, pancreatitis.

Not known: Ischaemic colitis

Hepato-biliary disorders

Common: Increased levels of transaminases (AST, ALT).

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Urticaria.

Very rare: Bullous dermatitis, Eczema, erythema, erythema multiforme, erythroderma (exfoliative dermatitis), alopecia, photosensitivity reactions, purpura, allergic purpura (Henoch-Schönlein), pruritus, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome).

Not known: Fixed drug eruption, generalised bullous fixed drug eruption

Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.

Renal and urinary disorders

Very rare: Acute renal insufficiency, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.

Reproductive system and breast disorders

Rare: impotence (causative relation to diclofenac unclear)

General disorders administration site conditions

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Rare: Tiredness, oedema.

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*

4.9 Overdose

Toxicity: Doses more than 300 mg could be toxic. Administration of 50 mg to children aged 1–3 years gave no or only mild intoxication. Administration of 150 mg followed by activated charcoal tablets to a 2-year-old gave mild intoxication. Administration of 325 mg to an adult gave moderate intoxication. Administration of 2.8 g during one week resulted in intestinal perforation of an adult, 2 g to an adult

gave renal effects.

Symptoms: There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as nausea, vomiting, abdominal pain, gastrointestinal haemorrhage, diarrhoea, dizziness, somnolence, headache, tinnitus, anxiety, hallucinations, convulsions, kidney dysfunction, in some cases liver dysfunction, tendency to oedema and possibly also metabolic acidosis. In the event of significant poisoning, acute renal failure and liver damage are possible.

Treatment: Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose. Antacids if required, which may be supplemented with sucralfate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory/antirheumatic drugs (NSAIDs).
ATC code: M01AB05.

Diclofenac Bluefish contains the sodium salt of diclofenac, a non-steroidal substance with anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin synthesis has been shown experimentally to be an important component of the mechanism of action. Prostaglandins play a prominent role in inflammation, pain and fever. This means that diclofenac also inhibits platelet aggregation. Diclofenac exhibits anti-inflammatory and analgesic properties in rheumatic diseases, clinically manifested as relief of symptoms such as pain when resting and in motion, early morning stiffness and swollen joints. These properties are also manifested as improvement in function.

Diclofenac has been shown in clinical trials to relieve pain and reduce blood volumes in primary dysmenorrhoea.

Diclofenac inhibits renal prostaglandin synthesis. This effect is not significant in patients with normal renal function. The inhibition of prostaglandin synthesis can, however, lead to acute renal insufficiency, fluid retention and heart failure in patients with chronic renal, cardiac or liver insufficiency and with conditions that change plasma volume (see Section 4.3).

There is limited experience from clinical trials regarding the use of diclofenac in paediatric patients with JRA/JIA.

In a randomized, double-blind, parallel, 2-week group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of a daily dose of diclofenac, 2-3 mg/kg body weight, acetylsalicylic acid ASA, 50 100 mg/ kg body weight/day, and placebo was compared - 15 patients in each group.

Overall, 11 of 15 diclofenac patients, 6 of 12 acetylsalicylic acid patients, and 4 of 15 placebo patients showed a statistically significant improvement ($p < 0.05$).

The number of tender joints decreased with diclofenac and ASA but increased with placebo.

In another randomized, double-blind, parallel, 6-week group study in children aged 4-15 years with

JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg body weight, n=22) was comparable to indomethacin (daily dose 2-3 mg/kg body weight, n=23).

5.2 Pharmacokinetic properties

Diclofenac is absorbed quickly and completely from the gastro-resistant tablet after passing through the stomach. Where a tablet has been taken with or after a meal, passage through the stomach is slower than if the tablet is taken before a meal, but the amount of active substance absorbed is the same. Bioavailability is around 50% after oral administration on account of first-pass metabolism in the liver. The peak plasma concentration is 1.5 µg/ml (5 µmol/l) and is reached an average of two hours after intake of a 50 mg tablet. Plasma concentration is linearly related to dosage.

The active substance is eliminated from plasma with a total clearance of 263 ±56 ml/min. The half-life is 1-2 hours.

The peak concentration of diclofenac in the synovial fluid is reached 2-4 hours after the peak plasma concentration. Half-life in the synovial fluid is 3-6 hours. The concentration of active substance is higher in the synovial fluid than in plasma just 4-6 hours after intake and remains higher for up to 12 hours.

Diclofenac has a serum protein binding rate of 99.7% and binds primarily to albumin (99.4%).

The biotransformation of diclofenac occurs partly through glucuronidation of the intact molecule by UGT2B7, but mainly through single and multiple hydroxylations and methoxylation by CYP2C9 isoenzymes, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active but to a much lesser extent than diclofenac. Approximately 60% of the dose administered is eliminated in urine in the form of metabolites. Less than 1% is excreted unchanged. The rest of the dose is eliminated as metabolites in bile and faeces.

The pharmacokinetic properties are unchanged following repeated administration.

No accumulation occurs in the recommended dosage interval.

The age of the patient has no effect on the absorption, metabolism or excretion of diclofenac.

Special patient groups

In patients with impaired kidney function, no accumulation of the unchanged active substance has been seen following a single dose. With a creatinine clearance of less than 10 ml/min, the theoretical plasma level of metabolites at steady state is approximately four times as high as in healthy volunteers. The metabolites are excreted in bile.

In patients with impaired liver function (chronic hepatitis, uncompensated cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

No additional preclinical information that is considered to be significant for clinical safety is available, apart from the information given in other parts of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

25 mg:

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, maize starch, macrogol, methacrylic acid-ethyl acrylate copolymer, dimethicone,

polysorbate 80, sorbic acid, talc, colourings (yellow iron oxide E172, titanium dioxide E171).

50 mg:

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, maize starch, macrogol, methacrylic acid-ethyl acrylate copolymer, dimethicone, polysorbate 80, sorbic acid, talc, colourings (red and yellow iron oxide E172, titanium dioxide E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister pack (PVC/PVDC/ALU):

25 mg gastro-resistant tablets: 10, 20, 30, 50 and 100

50 mg gastro-resistant tablets: 10, 20, 30, 50 and 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
10028 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2006-03-17

Date of latest renewal: 2010-05-30

10. DATE OF REVISION OF THE TEXT

1-SEP-2025