Product registration dossier

Diclofenac Sodium Suppositories 50mg

Submitted by

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1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Diclofenac Sodium Suppositories 12.5mg, 50mg, 100mg

2. Qualitative and quantitative composition

The active substance is sodium-|o-|(2,6-dichlorophenyl)-amino|-phenyl|-acetate (diclofenac sodium).

Each suppository contains 12.5mg, 50mg and 100mg diclofenac sodium.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Suppositories.

4. Clinical particulars

4.1 Therapeutic indications

Diclofenac Sodium Suppositories 25mg, 50mg and 100mg suppositories

Adults and Elderly:

Relief of all grades of pain and inflammation in a wide range of conditions, including:

(i) arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,

(ii) acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,

(iii) other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

Diclofenac Sodium Suppositories 50mg and 100mg suppositories are not indicated for use in children.

Diclofenac Sodium Suppositories 12.5mg and 25mg suppositories only

Children (aged 1-12 years): Juvenile chronic arthritis

Children (aged 6 years and above): As monotherapy or as adjunct therapy with morphine or other opiates (due to its opiate-sparing effect) for the relief of acute post-operative pain.

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).
Not to be taken by mouth, as per rectal administration only.
The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools.

Adults:
75-150mg daily, in divided doses (25mg, 50mg and 100mg suppositories only).
The recommended maximum daily dose of Diclofenac Sodium Suppositories is 150mg. This may be administered using a combination of dosage forms, e.g. tablets and suppositories. (25mg and 50mg suppositories only).
100mg suppositories may also be given as a once daily treatment, usually at night. Where necessary, therapy may be combined with 25mg or 50mg tablets or suppositories up to the maximum dose of 150mg per day.

Special populations
Elderly
Although the pharmacokinetics of Diclofenac Sodium Suppositories are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also Precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

Cardiovascular and significant cardiovascular risk factors
Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.3 Contraindications).
Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used and for the shortest duration possible (see section 4.4 Special warnings and precautions for use).

Renal impairment
Diclofenac is contraindicated in patients with renal failure (see section 4.3 Contraindications).
No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

Hepatic impairment

Diclofenac is contraindicated in patients with hepatic failure (see section 4.3 Contraindications).
No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.4 Special warnings and precautions for use).

Paediatric population
Children (aged 1-12 years) with juvenile chronic arthritis: 1-3mg/kg per day divided into 2 or 3 doses (12.5mg and 25mg suppositories only).
Children (aged 6-12 years) with acute post-operative pain: 1-2mg/kg per day in divided doses.
Treatment of acute post-operative pain should be limited to 4 days treatment (12.5mg and 25mg suppositories only).

4.3 Contraindications
- Hypersensitivity to the active substance or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6 Ferility, pregnancy and lactation)
- Hepatic failure
- Renal failure
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- Proctitis

4.4 Special warnings and precautions for use
General
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 Posology and method of administration and GI and cardiovascular risks below).
The concomitant use of Diclofenac Sodium Suppositories 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 (see section 4.5 Interactions with other medicaments and other forms of interaction).

Caution is indicated in the elderly on basic medical grounds. 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 Posology and Method of administration).

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects). 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.

Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties.

Gastrointestinal effects:
Gastrointestinal bleeding (haematemesis, melaena) ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.
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 disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2 Posology and method of administration).

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk. (See section 4.5 Interactions with other medicaments and other forms of interaction).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see section 4.5 Interaction with other medicaments and other forms of interaction).

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

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.

Hepatic effects:
Close medical surveillance is required when prescribing Diclofenac Sodium Suppositories to patients with impairment of 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, regular monitoring of hepatic function is indicated as a precautionary measure.

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenac Sodium Suppositories should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

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

Renal effects:
As fluid retention and oedema have been reported in association with NSAIDs 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 those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3

Contraindications). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation 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 and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Diclofenac Sodium Suppositories (see section 4.8 Undesirable effects). Patients appear to be at the 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. Diclofenac Sodium Suppositories should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Cardiovascular and cerebrovascular effects:
Patients with congestive heart failure (NYHA-I) or 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.

Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac.

Clinical trial and epidemiological data consistently point towards 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.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

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

Diclofenac Sodium Suppositories may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5 Interaction with other medicaments and other forms of interactions). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities 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.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:
The use of Diclofenac Sodium Suppositories may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac Sodium Suppositories should be considered (see section 4.6 Pregnancy and Lactation).

Excipient(s) with known effect
This medicine contains less than 1mmol sodium (23mg) per suppository, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction
The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.
Lithium:
If used concomitantly, Diclofenac Sodium Suppositories may increase plasma concentrations of lithium Monitoring of the serum lithium level is recommended.
Digoxin:
If used concomitantly, Diclofenac Sodium Suppositories may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents:
Like other NSAIDs, concomitant use of Diclofenac Sodium Suppositories with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.
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 periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia:
Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly (see section 4.4 Special warnings and precautions for use). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids:
Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4 Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs):
Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics:
Clinical studies have shown that Diclofenac Sodium Suppositories can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate:
Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing

methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin:

Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus:

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials:

Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Phenytoin:

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

Colestipol and cholestyramine:

These agents can induce a delay or decrease in absorption of diclofenac. Therefore, itis recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

Cardiac glycosides:

Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone:

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

Potent CYP2C9 inhibitors:

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

4.6 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 or 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 shown to result in increased pre-and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. From the 20th week of pregnancy onward, Diclofenac Sodium Suppositories 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 arterious constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Diclofenac Sodium Suppositories should not be given unless clearly necessary. If Diclofenac Sodium Suppositories is used by a woman attempting to conceive, or during the first or 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 for several days from gestational week 20 onward. Diclofenac Sodium Suppositories should be discontinued if oligohydramnios or ductus arteriosus constriction is found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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, Diclofenac Sodium Suppositories is contra-indicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, Diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

Female fertility

As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered. See also section 4.4 Special warnings and

precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

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

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, leucopenia, anemia (including hemolytic anemia and aplastic anaemia), agranulocytosis.
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, nightmares, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence, tiredness.
Very rare:	Paraesthesia, memory impairment, convulsions, anxiety, tremor, asepticmeningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare:	Visual disturbance, vision blurred, diplopia.

Unknown	Optic neuritis.
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain
Not known	Kounis syndrome.
Vascular disorders	
Very rare:	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnoea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare:	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoeahaemorrhagic, melaena, gastrointestinal ulcer with or without bleeding orperforation (sometimes fatal particularly in the elderly).
Very rare:	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitisor Crohn's disease), constipation, stomatitis (including ulcerativestomatitis), glossitis, oesophageal disorder, diaphragm-like intestinalstrictures, pancreatitis.
Unknown	Ischaemic colitis.
Hepatobiliary disorders	
Common:	Transaminases increased
Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders	
Common:	Rashes.
Rare:	Urticaria
Very rare:	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome),dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute renal failure, haematuria, proteinuria, nephrotic syndrome,interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Very rare:	Impotence.
General disorders and administration site conditions	
Rare:	Application site irritation, oedema

* The frequency reflects data from long-term treatment with a high dose (150 mg/day).

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 doses (150mg daily)and in long term treatment (see sections 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use)

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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.

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures

Patients should be treated symptomatically as required. Within one hour of ingestion

of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults gastric lavage should be considered within one hour of ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties

In 15 clinical studies involving the use of rectal diclofenac in the treatment of postoperative pain in children with an overall mean age of 8 years, the use of rescue analgesia (particularly opiates) was reduced. (12.5mg and 25mgsuppositories only)

Pharmacotherapeutic group

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Mechanism of action

Diclofenac Sodium Suppositories is a nonsteroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

12.5mg/25mg Suppositories only

There is a limited clinical trial experience of the use of diclofenac in JRA/JIA paediatric patients. In a randomised, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p \leq 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomised, double-blind, 6 week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3 mg/kg BW, (n=23).

5.2 Pharmacokinetic properties

There is limited kinetic data from 6 children aged 6-16 years with juvenile chronic arthritis who received a once daily dose of diclofenac for 2 weeks. When corrected for a body weight of 75kg, kinetic parameters were similar to those in adults. (12.5mg and 25mg suppositories only)

Absorption

Absorption is rapid; although the rate of absorption is slower than from enteric-coated

tablets administered orally. After the administration of 50mg suppositories, peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of enteric-coated tablets (1.95 = 0.8 µ g/ml (1.9 µ g/ml = 5.9 µ mol/l)).

Bioavailability

As with oral preparations the AUC is approximately a half of the value obtained from a parenteral dose.

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

The plasma concentrations attained in children given equivalent doses (mg/kg, b.w.) are similar to those obtained in adults. (12.5mg and 25mg suppositories only)

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose (see section 4.6 Pregnancy and lactation).

Metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination

The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

Patients with renal impairment:

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

Patients with hepatic disease:

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

Diclofenac Sodium Suppositories 12.5mg

Hard fat (No.36)
Hard fat (No.38)
Polyethylene glycol 400 (PEG400)

Diclofenac Sodium Suppositories 50mg

Hard fat (No.36)
Hard fat (No.38)
Polyethylene glycol 400 (PEG400)

Diclofenac Sodium Suppositories 100mg

Hard fat (No.36)
Hard fat (No.38)
Polyethylene glycol 400 (PEG400)

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

The suppositories are Off-white to light yellow, torpedo-shaped, with smooth or slightly rough surfaces and a slightly fatty odour, and are sealed in a composite foil made of polyvinylchloride (PVC) laminated with low-density polyethylene (LDPE).
Box of 10 suppositories.

6.6 Special precautions for disposal and other handling

For rectal use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Maltobic Pharmaceutical Company Nigeria Limited
15, Orlu Street, Fegge Onitsha, Anambra state, Nigeria