Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceclova 75 mg/20 mg modified-release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release hard capsules contains 75 mg diclofenac sodium (25 mg as gastro-resistant pellets and 50 mg as prolonged release pellets) and 20 mg of omeprazole (gastro-resistant pellets).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release capsule, hard.

Elongated 20.7 mm x 6.9 mm hard gelatine capsules with pink opaque cap and yellow opaque body, filled with white to light yellow pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceclova is indicated for symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in adult patients at risk of developing NSAID associated gastric and/or duodenal ulcers, who are adequately controlled with diclofenac and omeprazole.

4.2 Posology and method of administration

Posology

Adults
The dose is one capsule daily (diclofenac 75 mg/ omeprazole 20 mg).
In patients switching to Ceclova the symptoms should be adequately controlled with separately administered monocomponent preparations of the same doses as contained in this combination. If symptoms are not controlled by a once daily dosing, the therapy regime must be changed by switching to one or more alternative products. Patients should not take more than one capsule of Ceclova per day, as this would lead to over-exposure to omeprazole.
Undesirable effects may be minimised by using the shortest duration necessary to control symptoms (see section 4.4).

Treatment should be continued to achieve individual treatment goals, reviewed at regular intervals and discontinued if no benefit seen.

Special populations

Patients with renal impairment
In patients with mild to moderate renal impairment Ceclova should be used cautiously and renal function should be monitored closely (see section 5.2).
Ceclova is contraindicated in patients with severe renal impairment (see section 4.3 and 4.4).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment Ceclova should be used cautiously and hepatic function should be monitored closely.
Ceclova is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).

Elderly (> 65 years)

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. (see sections 4.4 and 5.2).

Paediatric population (≤ 18 years)
Ceclova is not recommended for use in children, due to lack of data on safety and efficacy.

Method of administration

Ceclova should be swallowed whole with a liberal quantity of liquid.

Ceclova should be taken preferably with food.

Monitoring of treatment
In the case of long-term treatment with Ceclova, laboratory blood counts and liver and kidney function should be monitored.

4.3 Contraindications

Hypersensitivity to the active substances, substituted benzimidazoles or to any of the excipients listed in section 6.1.

Previous hypersensitivity reactions (eg asthma, urticaria, angioedema or rhinitis) in response to ibuprofen, aspirin or other NSAIDs.

Severe hepatic, renal and cardiac failure (See section 4.4).

During the last trimester of pregnancy (See section 4.6).

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.

Ceclova, like other proton pump inhibitors (PPIs) containing medicine must not be used concomitantly with nelfinavir (see section 4.5).

Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Conditions characterized by an increased bleeding tendency.

4.4 Special warnings and precautions for use

Diclofenac (NSAIDs)

In all patients:
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).
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without previous 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. Ceclova may mask the signs and symptoms of infection due to its pharmacodynamic properties.
The use of Ceclova with concomitant NSAIDs including cyclo-oxygenase 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).

Elderly:
Caution is indicated on basic medical grounds. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2). It is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Respiratory disorders:
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 to 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 a medical emergency). This is also applicable to patients who are known to be allergic to other substances and have previously presented with skin reactions, pruritus or urticaria.

Cardiovascular, Renal and Hepatic Impairment:
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.
Close medical surveillance is required when prescribing Diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.
As with other NSAIDs, treatment with Diclofenac can be associated with a rise in liver enzymes. During prolonged treatment with Diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, or 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 without prodromal symptoms. Caution is called for in patients with hepatic porphyria, since it may trigger an attack.
Fluid retention and oedema have been reported with NSAID therapy, including diclofenac; particular caution is called for in patients with impaired cardiac or renal function, a 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 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (See section 4.3).

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 dose (150 mg 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 with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (eg hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:
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 serious 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. To reduce the risk of GI toxicity in these patients the treatment should be initiated and maintained at the lowest effective dose.

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 medicinal products which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (See section 4.5). When GI bleeding or ulceration occurs in patients receiving Ceclova, the treatment should be withdrawn. Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8).

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).

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).

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. Ceclova should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Haematological Effects:
Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.
Use of Ceclova is recommended only for short term treatment. During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Omeprazole
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e. g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.
Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and in hospitalised patients, possibly also Clostridium difficile (see section 5.1).
As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Renal impairment
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking omeprazole and may occur at any point during omeprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.
Omeprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Diclofenac (NSAIDs)

Other analgesics including cyclo-oxygenase-2 selective inhibitors:
Avoid concomitant use of two or more NSAIDs (including acetylsalicylic acid) as this may increase the risk of adverse effects (See section 4.4).

Diuretics, ACE inhibitors and Angiotensin-II Antagonists:
Reduced diuretic and anti-hypertensive effect may be seen.

The combination should be administered with caution, and patients, especially the elderly, should have their blood pressure monitored. Patients should be adequately hydrated and renal function monitored after initiation of concomitant therapy and periodically thereafter, particularly for those patients on diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity.

Diuretics can increase the risk of nephrotoxicity of NSAIDs. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

Cardiac glycosides:
NSAIDs may exacerbate cardiac failure, reduced GFR (Glomerular Filtration Rate) and increase plasma glycoside levels.

Lithium:
Decreased elimination of lithium, may occur and monitoring of serum lithium levels is necessary.

Ciclosporin:
Increased risk of nephrotoxicity, therefore diclofenac should be given at doses lower than those that would be used in patients not receiving ciclosporin.

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

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding (See section 4.4).

Anticoagulants and anti-platelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see 4.4). Although clinical studies do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving concomitant diclofenac and anticoagulants. Close monitoring of such patients is therefore recommended.

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.

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

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

Colestipol and cholestyramine:
These agents can induce a delay or decrease in absorption, therefore,it is recommended that diclofenac is administered at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

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

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

Digoxin:
A rise in plasma concentrations of digoxin may be seen, therefore monitoring of serum digoxin levels is recommended.

Methotrexate:
Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other. Diclofenac can inhibit the tubular renal clearance of methotrexate thereby increasing methotrexate levels, leading to toxicity.

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

Phenytoin:
Monitoring of phenytoin plasma concentrations recommended due to an expected increase in phenytoin levels.

Omeprazole

Effects of omeprazole on the pharmacokinetics of other active substances

Active substances with pH dependent absorption
The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Nelfinavir, atazanavir:
The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated (see section 4.3). Coadministration of omeprazole (40 mg once daily) reduced mean nelvinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75 –90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended (see section 4.4). Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The coadministration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

Digoxin:
Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Clopidogrel:
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged (see section 4.4).

Other active substances:
The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19:
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

Cilostazol:
Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Phenytoin:
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism

Saquinavir:
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Methotrexate:
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

Tacrolimus:
Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors CYP2C19 and/or CYP3A4:
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit
CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4:

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Diclofenac
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-foetal death.

In addition, increased incidences of various malformations, including cardiovascular malformations, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, Ceclova 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, Ceclova should not be given unless clearly necessary. If Ceclova 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 Ceclova for several days from gestational week 20 onward. Ceclova should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

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

the mother and the neonate, at the end of 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, Ceclova is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Omeprazole
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.

Breast-feeding:

Diclofenac
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should not be administered during breast-feeding in order to avoid undesirable effects in the infant.

Omeprazole
Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

Fertility:

Diclofenac
The use of diclofenac 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 Ceclova should be considered.

Omeprazole
Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue, and visual disturbances, vertigo, somnolence or other central nervous system disturbances are possible after taking NSAIDs. Dizziness and visual disturbances may occur after taking omeprazole (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

If serious side-effects occur, Ceclova should be withdrawn.
Adverse reactions from diclofenac and from omeprazole in clinical trials, epidemiological data and post marketing are summarised in the table below.
For Diclofenac the most commonly observed adverse events are gastrointestinal in nature.
For Omeprazole, the identified adverse drug reactions were not found to be dose-related. The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following terminologies have been used in order to classify the occurrence of adverse reactions:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Frequency	**Diclofenac**	**Omeprazole**
Blood and lymphatic system disorders		
Rare		Leukopenia, thrombocytopenia
Very rare	Leucopenia, neutropenia, thrombocytopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis	Agranulocytosis, pancytopenia
Immune system disorders		
Rare	Non-specific allergic reactions, anaphylactoid reactions (including hypotension and shock) and anaphylaxis. Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Very rare	Angioedema,	

	angioneurotic oedema (including face oedema)	
Metabolism and nutrition disorders		
Rare		Hyponatraemia
Not known		Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders		
Uncommon		Insomnia
Rare		Agitation, confusion, depression
Very rare	Depression, disorientation, insomnia, irritability, psychotic reactions, nightmares	Aggression, hallucinations
Nervous system disorders		
Common	Headache, dizziness	Headache
Uncommon		Dizziness, paraesthesia, somnolence
Rare	Somnolence	Taste disturbance
Very rare	Memory disturbance, paraesthesia, aseptic meningitis (especially in patients with existing auto-immune disorders, such as lupus erythematosus, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation. Confusion, hallucinations, malaise, fatigue and drowsiness, taste disturbances, tremor, convulsions, anxiety, cerebrovascular accident.	
Eye disorders		
Rare		Blurred vision
Very rare	Visual disturbance (blurred vision), diplopia, optic	

	neuritis	
Ear and labyrinth disorders		
Common	Vertigo	
Uncommon		Vertigo
Very rare	Impaired hearing, tinnitus	
Cardiac disorders		
Rare	Oedema	
Very rare	Hypertension, vasculitis, palpitations, chest pain, cardiac failure	
Not known	Kounis syndrome	
Vascular disorders		
Very rare	Small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)	
Respiratory, thoracic and mediastinal disorders		
Rare	Asthma (including dyspnoea)	Bronchospasm
Very rare	Pneumonitis	
Gastrointestinal disorders		
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare	Gastritis, haematemesis, haemorrhagic diarrhoea, melaena, gastrointestinal ulcer (with or without bleeding or perforation), peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly	Dry mouth, stomatitis, gastrointestinal candidiasis
Very rare	Exacerbation of colitis and Crohn's disease,	

	constipation, ulcerative stomatitis, glossitis, oesophageal disorder, diaphragm like intestinal strictures, pancreatitis	
Not known		Microscopic colitis
Hepatobiliary disorders		
Common	Increased transaminases	
Uncommon		Increased liver enzymes
Rare	Jaundice, abnormal liver function, hepatitis (in isolated cases fulminant)	Hepatitis with or without jaundice
Very rare	Hepatic necrosis, hepatic failure	Hepatic failure, encephalopathy in patients with preexisting liver disease
Skin and subcutaneous tissue disorders		
Common	Rash	
Uncommon		Dermatitis, pruritus, rash, urticaria
Rare	Urticaria	Alopecia, photosensitivity
Very rare	Photosensitivity, skin eruptions, Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), loss of hair, dermatitis exfoliative, purpura, allergic purpura, pruritus	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known		Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders		
Uncommon		Fracture of the hip, wrist or spine
Rare		Arthralgia, myalgia
Very rare		Muscular weakness
Renal and urinary disorders		
Rare		Tubulointerstitial nephritis (with possible progression to renal failure)
Very rare	Nephrotoxicity in various forms, including interstitial nephritis, proteinuria, renal papillary necrosis, nephrotic syndrome, acute	

	renal failure, urinary abnormalities (e.g. haematuria)	
Musculoskeletal and connective tissue disorders		
Uncommon		Fracture of the hip, wrist or spine
Rare		Arthralgia, myalgia
Very rare		Muscular weakness
Reproductive system and breast disorders		
Very rare		Gynaecomastia
General disorders and administration site conditions		
Uncommon		Malaise, peripheral oedema
Rare		Increased sweating

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).

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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Diclofenac

Symptoms:
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting and occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

Treatment:
Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. 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 a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be closely monitored for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition. Specific therapies such as forced diureses, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Omeprazole

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Acetic acid derivatives and related substances ATC code: M01AB55 (diclofenac, combinations)

Diclofenac

Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

Omeprazole

Mechanism of action
Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing. Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H^+ K^+ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dosedependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

Pharmacodynamic effects
All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

Effect on gastric acid secretion:
Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and nighttime gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of ≥ 3 for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the esophagus in patients with gastro-esophageal reflux disease. The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time. No tachyphylaxis has been observed during treatment with omeprazole.

Other effects related to acid inhibition:
During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and inhospitalised patients, possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

5.2 Pharmacokinetic properties

Diclofenac

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Therapeutic plasma concentrations occur about ½ hour after administration of diclofenac. The active substance is 99.7% protein bound and the plasma half-life for the terminal elimination phase is 1-2 hours.

Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form. Following rapid gastric passage, the gastro-resistant pellet component of diclofenac ensures quick availability of the active component in the blood stream. The prolonged release pellets cause a delayed release of the active component, which means one single daily dose is usually sufficient.

Special populations
Patients with renal impairment
Diclofenac is known to be substantially excreted by the kidney therefore the risk of toxic reactions to Ceclova may be greater in patients with impaired renal function.

Omeprazole

Absorption
Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as entericcoated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution
The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism
Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

Elimination
The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dosedependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone). No metabolite has been found to have any effect on gastric acid secretion.

Special populations

Impaired hepatic function
The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.

Impaired renal function
The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly
The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

5.3 Preclinical safety data

Diclofenac

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

Omeprazole

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H_2-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content:
Microcrystalline cellulose
Povidone
Colloidal anhydrous silica
Methacrylic acid ethyl acrylate copolymer (1:1), Type A
Propylene glycol
Ammonio methacrylate copolymer type A
Ammonio methacrylate copolymer type B
Mannitol
Magnesium carbonate heavy
Hydroxypropylcellulose
Sodium laurilsulfate
Hypromellose
Polysorbate 80
Triethyl citrate
Talc

Capsules shell:

Titanium dioxide (E171)
Iron oxide red E 172
Iron oxide yellow E 172
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE Bottle/Blister: 4 years

Shelf life after first opening
HDPE Bottle: 1 month
For storage conditions after first opening of the medicinal product, see section 6.4.

6.4 Special precautions for storage

HDPE Bottle/Blister: Do not store above 30 °C.

HDPE Bottle: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

White HDPE bottle with a tamper-evident polypropylene screw cap with integrated desiccant. Original packages of 30 modified-release capsules, hard

oPA-Aluminium-PVC / Aluminium Blister
Original packages of 10, 20, 30, 50, 60, 100 modified release capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Aenova IP GmbH
Temmlerstrasse 2
Marburg
Hassia
35039
Germany

8 MARKETING AUTHORISATION NUMBER

PA22984/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th July 2018
Date of last renewal: 17th July 2023

10 DATE OF REVISION OF THE TEXT

November 2023