SUMMARYOFPRODUCTCHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dynapar EC 50mgenteric coatedtablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains Diclofenac Sodium 50 mg.

Excipients with known effect: Lactose.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric Coated Tablets.
Brown coloured, round shaped, biconvex, enteric coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reliefofallgradesofpainandinflammationin awiderangeofconditions,including:

(i) arthriticconditions:rheumatoidarthritis,osteo-arthritis, ankylosing spondylitis, acute gout,

(ii) acutemusculo-skeletaldisorderssuchasperiarthritis(forexamplefrozen shoulder), tendinitis, tenosynovitis,bursitis,

(iii) otherpainfulconditionsresultingfromtrauma,includingfracture, lowback pain,sprains, strains, dislocations, orthopaedic, dentaland other minor surgery.

4.2 Posology and method of administration

Undesirableeffects maybeminimised byusingthelowest effectivedosefor the shortest duration necessarytocontrol symptoms (see section 4.4).

Fororaladministration.
To betakenpreferablywithorafterfood.

Adults: 75-150 mgdailyintwo orthree divided doses
Therecommended maximumdailydose is150 mg.

Specialpopulations

Elderly
Althoughthepharmacokineticsofdiclofenacarenotimpairedtoanyclinically relevantextentin elderlypatients,nonsteroidalanti-inflammatorydrugsshouldbe used with particularcautionin such patientswho generallyare more prone to adverse reactions.In particularitisrecommendedthatthelowesteffectivedosagebeusedin frailelderlypatientsorthose witha low bodyweight (see also section4.4)andthe patient should bemonitored regularlyfor GIbleedingduringNSAID therapy.

Cardiovascular and significant cardiovascularriskfactors

Diclofenac is contraindicated in patients with established congestive heart failure (NYHAII-IV),ischemic heart disease,peripheral arterialdisease and/or cerebrovasculardisease(seesection 4.3 Contraindications).

Patientswith congestiveheartfailure(NYHA-I)or significantriskfactorsfor cardiovasculardiseaseshouldbetreatedwithdiclofenaconlyaftercareful consideration. Since cardiovascularrisks with diclofenac mayincrease with doseand durationofexposure,thelowesteffectivedailydoseshouldbeused andforthe shortestdurationpossible (see section4.4 Special warningsand precautions for use).

Renalimpairment

Diclofenaciscontraindicatedinpatientswithsevere renalimpairment(seesection 4.3).Nospecificstudieshavebeencarriedoutinpatientswithrenalimpairment, therefore,no specific doseadjustment recommendations canbe made. Cautionis advisedwhenadministeringdiclofenactopatientswith mildtomoderaterenal impairment(seesection4.3and4.4).

Hepaticimpairment

Diclofenaciscontraindicatedinpatientswithsevere hepaticimpairment(seesection 4.3).Nospecificstudieshavebeencarriedoutinpatientswithhepaticimpairment, therefore,no specific doseadjustment recommendations canbe made. Cautionis advised whenadministeringdiclofenactopatients with mild to moderate hepatic impairment (see section4.3and 4.4).

Paediatricpopulation

For children over 14years of age, the recommended dailydose is 75-100mg in two or three divided doses. Diclofenac tablets are not recommended for children under 14years ofage.

4.3 Contraindications

Knownhypersensitivitytotheactivesubstanceortoanyoftheexcipients.

Activegastricorintestinalulcer,bleedingorperforation.

Historyofgastrointestinalbleedingorperforation,relatedto previousNSAIDs therapy.

Active,orhistoryofrecurrentpepticulcer/haemorrhage(twoormoredistinctepisodesof proven ulceration, perforation or bleeding).

Last trimester of pregnancy (see section 4.6)

Severe hepatic, renal or cardiac failure (see section 4.4).

Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, acute rhinitis or angioedema are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs.

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

4.4 Special warnings and precautions for use

General

Undesirableeffectsmaybeminimisedbyusingthelowesteffectivedoseforthe shortestdurationnecessaryto controlsymptoms(see section 4.2, and GIand cardiovascularrisksbelow).

The concomitant useof diclofenacwith systemicNSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of anyevidencedemonstratingsynergisticbenefits and thepotential for additive undesirable effects (see section 4.5).

Caution is indicated in the elderlyon basic medical grounds.In particular, itis recommended that the lowest effective dose beused in frail elderlypatients or those with a low bodyweight (see section 4.2).

As with other NSAIDs includingdiclofenac,allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlierexposure to thedrug (seesection 4.8). Hypersensitivityreactions can also progress to Kounis syndrome,a serious allergic reaction that can result in myocardial infarction. Presentingsymptoms of such reactions can include chest pain occurringin association with an allergicreaction to diclofenac.

Like other NSAIDs, Diclofenac maymask the signs and symptoms of infection due to its pharmacodynamic properties.

Patientswith rarehereditaryproblems of galactose intolerance, the LAPP lactase deficiencyorglucose-galactosemalabsorption shouldnot takethis medicine asit containslactose.

Thetabletscontain methyland propyl parahydroxybenzoate which maycause allergic reactions(possiblydelayed).

This medicinecontainslessthan 1mmol sodium(23mg) pertablet,thatistosay essentially'sodiumfree'.

Gastrointestinaleffects

Gastrointestinalbleeding, ulcerationor perforation, which can befatal, has been reported with all NSAIDs, includingdiclofenac, and mayoccur atanytimeduring treatment,withorwithoutwarningsymptomsorapreviushistoryofserious gastrointestinalevents.They generallyhavemoreseriousconsequencesintheelderly. Ifgastrointestinalbleedingorulcerationoccursinpatientsreceivingdiclofenac,the medicinal product should bewithdrawn.

AswithallNSAIDs, includingdiclofenac,closemedical surveillanceisimperative and particularcaution should be exercised when prescribingdiclofenacin patients withsymptomsindicativeofgastrointestinal(GI)disordersorwithahistory suggestive ofgastricorintestinalulceration,bleeding orperforation(seesection 4.8).

The risk of GIbleeding,ulceration or perforation is higher with increasing NSAID doses including diclofenacand in patients with a historyof ulcer, particularlyif complicated with haemorrhage or perforation. The elderlyhave an increased frequencyofadversereactions to NSAIDs especially gastrointestinal bleeding and perforation which maybefatal (see section 4.2).

To reduce the risk of GItoxicityin patients with ahistoryof ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at thelowest effective dose.

Combinationtherapywithprotective agents(e.g. proton pump inhibitors or misoprostol)shouldbeconsideredforthesepatients, andalsoforpatientsrequiring concomitantuse ofmedicinal productscontainginglow-dose acetylsalicylic acid (ASA)/aspirin,orothermedicinalproductslikelytoincreasegastrointestinalrisk(see section4.5).

PatientswithahistoryofGItoxicity,particularlythe elderly, shouldreportany unusualabdominalsymptoms(especiallyGIbleeding).

Caution isrecommended inpatients receivingconcomitantmedicationswhich could increasetheriskofulcerationorbleeding,such assystemiccorticosteroids, anticoagulants such aswarfarin, selectiveserotonin-reuptake inhibitorsor anti-plateletagentssuchasaspirin(seesection4.5).

Close medical surveillance andcaution should also be exercised in patients with ulcerative colitis orCrohn’s disease, as these condition maybe exacerbated(see section4.8).

NSAIDs, includingdiclofenac, maybe associatedwith increasedrisk ofgastro-intestinal anastomoticleak. Closemedicalsurveillanceand cautionare recommendedwhen usingdiclofenacaftergastro-intestinal surgery.

Hepatic effects

Closemedical surveillanceis required when prescribingdiclofenacto patients with impaired hepatic function, as their condition maybeexacerbated.

As with other NSAIDs, includingdiclofenac, values of one or moreliver enzymes mayincrease. Duringprolonged treatment with diclofenac, regular monitoringof hepaticfunction is indicated as a precautionarymeasure.If abnormal liver function testspersist or worsen, ifclinical signs or symptoms consistent with liver disease develop orif other manifestations occur (eosinophilia, rash), diclofenac should bediscontinued. Hepatitis mayoccur with use of diclofenacwithout prodromal symptoms. Caution is called for when using Diclofenac in patients with hepaticporphyria, sinceit maytrigger an attack.

Renal effects

As fluidretentionand oedemahavebeen reported in association withNSAID therapy, includingdiclofenac,particularcautioniscalledforinpatientswithimpaired cardiacorrenalfunction,historyofhypertension,theelderly, patientsreceiving concomitanttreatmentwithdiureticsormedicinalproductsthatcansignificantly impactrenalfunction,andin thosepatientswithsubstantialextracellularvolume depletion fromanycause, e.g. beforeor after majorsurgery(see section 4.3). Monitoringofrenalfunctionisrecommendedasaprecautionarymeasurewhenusing Diclofenacinsuchcases.Discontinuationoftherapyisusuallyfollowedbyrecovery to the pre-treatmentstate.

Skin effects

Seriousskinreactions,someofthemfatal,includingexfoliativedermatitis,Stevens-Johnsonsyndrome, and toxic epidermal necrolysis, havebeen reported veryrarelyin association with the use ofNSAIDs includingdiclofenac (seesection 4.8). Patients appearto beathighestriskforthesereactionsearlyinthecourseoftherapy:theonset of thereaction

occurringinthemajorityofcaseswithinthefirstmonth oftreatment. Diclofenacshouldbediscontinuedatthefirstappearanceofskinrash,mucosal lesions,oranyothersign ofhypersensitivity.

Cardiovascular and cerebrovascular effects

Patients with congestiveheart failure(NYHA-I)orpatients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking)should onlybe treatedwith diclofenacafter careful consideration.

As the cardiovascularrisks of diclofenacmayincrease with doseand duration of exposure, the shortestduration possible and the lowest effectivedailydose should be used. The patient's need for symptomatic reliefand response to therapyshould be re-evaluated periodically.

Apopriate monitoringand advice are requiredfor patients with a historyof hypertension and/or mild to moderate congestiveheart failure (NYHA-I)as fluid retention and oedemahave been reported inassociation with NSAID therapyincludingdiclofenac.

Clinical trial and epidemiological dataconsistentlypoint towardsan increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use ofdiclofenac, particularlyat high dose(150mgdaily) and in longterm treatment.

Patientsshouldremainalertforthesignsandsymptomsofserious arteriothromboticevents(e.g.chestpain,shortnessofbreath,weakness,slurringof speech),whichcanoccurwithoutwarnings.Patientsshouldbeinstructedtoseea physician immediatelyin caseofsuchanevent.

Haematological effects

Use of Diclofenactablets50mgare recommendedonlyfor short term treatment.

Duringprolonged treatment with Diclofenac, as with other NSAIDs, monitoringof the blood count is recommended.

Like other NSAIDs, Diclofenac mayreversiblyinhibit platelet aggregation (see anticoagulants in section 4.5). Patients with defects of haemostasis, bleedingdiathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma

In patients with asthma, seasonal allergicrhinitis, swellingof thenasal mucosa(i.e. nasal polyps), chronic obstructive pulmonarydiseases or chronic infections of therespiratorytract (especiallyif linked to allergicrhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intoleranceto analgesics/analgesics-asthma), Quincke's oedemaor urticaria are morefrequent than inother patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicableas well for patients who areallergicto other substances, e.g. with skin reactions, pruritus or urticaria.

Caution is required if administered to patients sufferingfrom, orwith a previous historyofbronchial asthma, since NSAIDs have been reported to precipitate bronchospasm in such patients.

SLE and mixed connective tissue disease

In patients with systemiclupus erythematosus (SLE) and mixed connective tissuedisorders theremaybean increasedrisk ofasepticmeningitis (see section 4.8).

Femalefertility

Theuseof diclofenac mayimpair female fertilityand isnot recommended in women attemptingto conceive. Inwomen who havedifficulties conceivingor who are undergoinginvestigationofinfertility, withdrawalofdiclofenacshould beconsidered (seesection 4.6).

Long-termtreatment

All patients who are receivingnon-steroidalanti-inflammatoryagents should be monitored as a precautionarymeasuree.g. renal function, hepatic function (elevation of liverenzymes mayoccur) and bloodcounts. This is particularly important in the elderly.

4.5 Interaction with other medicinal products and other forms of interaction

Thefollowinginteractionsinclude thoseobservedwithDiclofenacgastro-resistant tabletsand/orotherpharmaceuticalformsofdiclofenac.

Lithium: Ifusedconcomitantly, diclofenacmayraiseplasmaconcentrationsof lithium. Monitoringofserumlithiumlevelisrecommended.

Digoxin: Ifusedconcomitantly,diclofenacmayraiseplasmaconcentrationsof digoxin.Monitoringoftheserumdigoxinlevelisrecommended.

Diuretics and antihypertensiveagents: Likeother NSAIDs, concomitantuseof diclofenacwithdiureticsorantihypertensiveagents(e.g. beta-blockers,angiotensin convertingenzyme(ACE)inhibitors)maycauseadecreaseintheirantihypertensive effectviainhibitionofvasodilatoryprostaglandinsynthesis.Thereforethe combination shouldbe administered withcaution and patients, especiallytheelderly, should havetheir blood pressureperiodicallymonitored. Patients should be adequatelyhydratedandconsiderationshouldbegiventomonitoringofrenal functionafterinitiationofconcomitanttherapyandperiodicallythereafter, particularlyfor diuretics and ACE inhibitorsduetotheincreasedriskof nephrotoxicity(seesection4.4).

Drugs known tocause hyperkalemia: Concomitant treatmentwithpotassium-sparingdiuretics,ciclosporin,tacrolimusortrimethoprimmaybeassociatedwith increased serumpotassiumlevels, whichshould therefore bemonitored frequently (seesection 4.4).

Other NSAIDsincludingcyclooxygenase-2 selectiveinhibitors and corticosteroids: Concomitantadministrationofdiclofenacandothersystemic NSAIDs(includingaspirin)orcorticosteroidsmayincreasethefrequencyof gastrointestinalundesirableeffectsbleedingorulceration(seesection4.4).Avoid concomitantuse oftwo ormore NSAIDs (see section4.4).

Anticoagulants andanti-platelet agents: Caution isrecommended since concomitantadministrationcouldincreasetheriskofbleeding(seesection4.4). Althoughclinicalinvestigationsdo notappeartoindicatethatdiclofenacaffectsthe actionofanticoagulants,therearereportsofanincreasedriskofhaemorrhagein patientsreceivingdiclofenacandanticoagulantsconcomitantly(seesection4.4). Therefore, to be certain thatno changein anticoagulantdosage isrequired,close monitoringofsuchpatientsisrequired.Aswithothernonsteroidalanti-inflammatory agents,diclofenacinahigh dosecanreversiblyinhibitplateletaggregation.

Selective serotoninreuptake inhibitors(SSRIs): Concomitantadministration of SSRIsmayincreasetheriskofgastrointestinalbleeding(seesection4.4).

Antidiabetics: ClinicalstudieshaveshownthatDiclofenac can begiven together withoral antidiabetic agentswithoutinfluencingtheirclinicaleffect.Howeverthere havebeenisolated

reports ofboth hypoglycaemic and hyperglycaemic effects necessitatingchangesinthedosageoftheantidiabeticagentsduringtreatmentwith diclofenac.Forthisreason,monitoringofthebloodglucoselevelisrecommendedas aprecautionarymeasureduringconcomitanttherapy.

Methotrexate: Diclofenaccaninhibitthetubularrenalclearanceofmethotrexate herebyincreasingmethotrexatelevels. Cautionisrecommended when NSAIDs, includingdiclofenac,areadministeredlessthan24hoursbeforetreatmentwith methotrexate,sincebloodconcentrationsofmethotrexatemayriseandthetoxicityof this substancebeincreased.Casesofserioustoxicity havebeen reportedwhen methotrexateand NSAIDs includingdiclofenacare given within24 hours ofeach other.Thisinteractionismediatedthroughaccumulationofmethotrexateresulting fromimpairmentofrenalexcretioninthepresenceoftheNSAID.

Ciclosporin: Diclofenac,likeother NSAIDs,mayincreasethenephrotoxicityof ciclosporin duetotheeffecton renalprostaglandins.Therefore, itshouldbe given at doseslowerthanthosethatwouldbeusedinpatientsnotreceivingciclosporin.

Quinoloneantibacterials:.Therehavebeenisolated reports ofconvulsions which mayhavebeen dueto concomitant use ofquinolones and NSAIDs. Convulsionsmay occurinpatientswithorwithoutapreviushistoryofepilepsyorconvulsions. Therefore, caution should beexercised when consideringthe useof aquinolone in patients who arealreadyreceivingan NSAID.

Phenytoin: When using phenytoin concomitantlywith diclofenac, monitoring of phenytoin plasma concentrationsis recommended due to an expected increase in exposure to phenytoin.

Colestipolandcholestyramine: Theseagentscaninduceadelayordecreasein absorption ofdiclofenac.Therefore, itis recommended to administer diclofenac at leastonehourbeforeor4to 6hoursafteradministrationofcolestipol/cholestyramine.

PotentCYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenacwith potent CYP2C9 inhibitors(such as voriconazole), which could result in a significant increase in peak plasmaconcentrations and exposure to diclofenac due to inhibitionof diclofenacmetabolism.

Mifepristone:NSAIDs should not beused for 8-12 daysafter mifepristone administration,as NSAIDs can reduce the effect ofmifepristone.

Cardiacglycosides: Concomitant use ofcardiac glycosidesand NSAIDs in patients mayexacerbatecardiacfailure,reduceGFRandincreaseplasmaglycosidelevels.

Tacrolimus:possibleincreasedriskof nephrotoxicitywhen NSAIDs are given with tacrolimus.Thismightbemediatedthroughrenalantiprostaglandineffectsofboth NSAID and calcineurininhibitor.

Zidovudine:increased risk of haematological toxicitywhen NSAIDs aregiven with zidovudine. There is evidence ofan increasedrisk of haemarthroses and haematoma in HIV (+) haemophiliacsreceivingconcurrent treatmentwith zidovudine and ibuprofen (a NSAID).

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis mayadverselyaffect the pregnancy and/or the embryo/foetaldevelopment. Datafromepidemiological studies suggest an increased riskof miscarriage and ofcardiac malformation and gastroschisis after use ofa prostaglandin synthesis inhibitor in early pregnancy.The absoluterisk of cardiovascular malformation was increased from less than 1%, up toapproximately1.5%. Therisk is believed to increase with dose and duration oftherapy.Inanimals, administration of a prostaglandin synthesis inhibitor has been shownto result in increased pre- and post-implantation loss and embryo-foetal lethality.

Inaddition, increased incidences ofvarious malformations, including cardiovascular, havebeen reported in animalsgiven a prostaglandin synthesis inhibitor duringthe organogenetic period.

From the 20th week of pregnancyonward, diclofenac use maycause oligohydramnios resultingfrom foetal renal dysfunction. This mayoccur shortlyafter treatment initiation and is usuallyreversible upon discontinuation. Inaddition, there havebeen reports ofductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, duringthe first and second trimester of pregnancy, diclofenac should not begiven unlessclearlynecessary.Ifdiclofenacis used byawoman attemptingto conceive, orduringthefirst or second trimesterof pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoringfor oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenacfor several

days from gestational week 20onward. Diclofenacshould be discontinued if oligohydramnios or ductus arteriosus constrictionare found.

Duringthe third trimesterof pregnancy, all prostaglandin synthesis inhibitors mayexpose the foetus to:

- cardiopulmonarytoxicity(with prematureconstriction of the ductus arteriosus and pulmonaryhypertension);
- renal dysfunction, which mayprogress to renal failure with oligo- hydroamniosis; the mother and the neonate, at the end of pregnancy,to:
- possible prolongation of bleedingtime, an anti-aggregatingeffect which mayoccur evenatverylow doses.
- inhibition of uterine contractions resultingin delayed or prolonged labour.

Consequently, diclofenacis contraindicated during the third trimester of pregnancy(see section 4.3 and 5.3).

Lactation

Likeother NSAIDs, diclofenac passes intothebreastmilkinsmallamounts. Therefore diclofenac should not beadministered duringbreastfeedingin orderto avoidundesirableeffectsintheinfant(seesection5.2).

FemaleFertility

As with other NSAIDs, theuseof diclofenacmayimpair femalefertilityand is not recommended in women attemptingto conceive.In women who have difficulties conceivingor who areundergoinginvestigation of infertility, withdrawal of diclofenacshould beconsidered(seealso section 4.4)

4.7 Effects on ability to drive and use machines

Patients experiencingvisual disturbances, dizziness, drowsiness, fatigue, vertigo, somnolence or other central nervous disturbances while taking diclofenac, should refrain from drivingorusing machines.

4.8 Undesirable effects

Ifseriousside-effects occur, Diclofenac should be withdrawn.

Adversereactions(Table1)arerankedunderheadingoffrequency, themostfrequent first,usingthefollowingconvention:verycommon:(>1/10);common(≥1/100, <1/10);uncommon(≥1/1,000, <1/100);rare(≥1/10,000,<1/1,000);veryrare (<1/10,000);notknown:cannotbeestimatedfromtheavailabledata.

The followingundesirableeffectsincludethosereportedwith eithershort-termor long-termuse.

Table 1

Blood andlymphatic system disorders	
Veryrare	Thrombocytopenia, neutropenia,leucopenia,anaemia(including haemolyticandaplasticanaemia), agranulocytosis
Immune system disorders	
Rare Veryrare	Hypersensitivity, anaphylacticand anaphylactoidreactions(including hypotension and shock) Angioneuroticoedema(includingface oedema).
Psychiatric disorders	
Veryrare	Disorientation,depression,insomnia,nightmares,irritability ,psychotic disorder.
Nervous system disorders	
Common Rare Veryrare Not known	Headache, dizziness. Somnolence,tiredness. Paraesthesia,memoryimpairment, convulsion, anxiety, tremor, aseptic meningitis tastedisturbances, cerebrovascularaccident. Disturbancesofsensation,confusion, hallucinations,malaise
Eyedisorders	

Veryrare Not known	Visualdisturbance, visionblurred diplopia. Opticneuritis.
Earand labyrinth disorders	
Common Veryrare	Vertigo. Tinnitus,hearingimpaired.
Cardiac disorders	
Uncommon* Not known	Palpitations, chest pain, cardiac failure, myocardial infarction. Kounis syndrome
Vasculardisorders	
Veryrare	Hypertension, vasculitis, hypotension.
Respiratory, thoracic andmediastinaldisorders	
Rare Veryrare Not known	Asthma(includingdyspnoea). Pneumonitis. Bronchospasm
Gastrointestinaldisorders	
Common Rare Veryrare Not known	Nausea, vomiting, diarrhoea, dyspepsia, abdominalpainflatulence,anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis,diarrhoeahaemorrhagic, melaena,gastrointestinalulcerwithor withoutbleedingorperforation, (sometimes fatal, particularlyin the elderly). Colitis (includinghaemorrhagiccolitis andexacerbationofulcerativecolitisor Crohn's disease), constipation, stomatitis (includingulcerativestomatitis), glossitis, oesophagealdisorder, oesophageallesions,diaphragm-like intestinalstrictures, pancreatitis, colonic damage. Ischaemic colitis
Hepatobiliary disorders	
Common Rare Veryrare Not known	Transaminasesincreased. Hepatitis,jaundice, liver disorder. Fulminanthepatitis,hepaticnecrosis, hepaticfailure Abnormalliverfunction.
Skin and subcutaneoustissue disorders	
Common Rare Veryrare	Rash Urticaria Bullouseruptions, eczema, erythema, erythemamultiforme,StevensJohnson Syndrome,toxicepidermalnecrolysis (Lyell's syndrome),

	dermatitis exfoliative,lossofhair,photosensitivity reaction,purpura,allergicpurpura, pruritis.
Renaland urinary disorders	
Veryrare	Acuterenalfailure,haematuria, proteinuria, nephroticsyndrome, interstitialnephritis,renalpapillary necrosis. Acute renal insufficiency.
General disorders and administration site conditions	
Rare	Oedema
Reproductivesystemandbreastdisorders	
Veryrare	Impotence
* *The frequencyreflects data fromlong-term treatmentwith ahigh dose (150 mg/day).*	

Clinical trial and epidemiological data consistentlypoint towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use ofdiclofenac, particularlyat high dose(150mgdaily) and in longterm treatment(see section 4.3 and 4.4).

4.9 Overdose

Symptoms

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

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentiallyconsists 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 high protein binding andextensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of apotentially life threatening overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antiinflammatory and Antirheumatic products, Non- steroids; Acetic Acid Derivatives and Related Substances
ATC Code: M01AB05
Diclofenac is a non-steroidal agent with marked analgesic, anti-inflammatory and anti-pyretic 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.

5.2 Pharmacokinetic properties

Absorption
Absorptioniscompletebutonsetisdelayed untilpassage through thestomach, which maybe affected byfood which delaysstomach empyting.The mean peakplasma diclofenacconcentrationreachedatabout 2 hours(50mgdose produces 1.48 ± 0.65µg/ml(1.5µg/ml ≡ 5µmol/l)).

Bioavailability
Abouthalfoftheadministereddiclofenacismetabolisedduringitsfirstpassage throughtheliver("firstpass" effect), theareaunder the concentrations curve (AUC) followingoraladministrationisabouthalfthatfollowinganequivalentparenteral dose.
Pharmacokinetic behaviourdoes not changeon repeated administration. Accumulation does not occur, providedtherecommended dosage intervals are observed.

Distribution

Theactive substanceis99.7% protein bound, mainlyto albumin (99.4%). Diclofenac wasdetectedina low concentration(100 ng/mL) in breast milkin one nursingmother.The estimated amountingested byan infantconsumingbreast milkis equivalentto a0.03 mg/kg/daydose (seesection 4.6).

Metabolism

Biotransformation ofdiclofenactakes place partlyby glucuronidationoftheintact molecule,butmainlybysingleandmultiplehydroxylationandmethoxylation, resultinginseveralphenolicmetabolites,mostofwhichareconvertedtoglucuronide conjugates.Twophenolicmetabolitesarebiologicallyactive,buttoamuchlesser extentthandiclofenac.

Elimination

Thetotalsystemicclearanceofdiclofenacinplasmais263± 56mL/min(meanvalue ±SD).Theterminalhalf-lifeinplasmais1-2hours.Fourofthemetabolites, includingthetwoactiveones,alsohaveshortplasmahalf-livesof1-3hours.

Repeated oraladministration of Diclofenac tabletfor 8daysin dailydoses of50 mgt i d does not leadto accumulation ofdiclofenacinthe plasma. About60%oftheadministereddoseisexcretedin theurineintheformofthe glucuronideconjugateoftheintactmoleculeandasmetabolites,mostofwhichare alsoconvertedto glucuronide conjugates.Lessthan 1%isexcretedas unchanged substance.Therestofthedoseiseliminatedasmetabolitesthroughthebilein the faeces.

Characteristicsin patients

Theageofthepatienthasno influenceon theabsorption,metabolismorexcretionof diclofenac.

*Patientswith renalimpairment:*In patientssuffering fromrenalimpairment,no accumulation ofthe unchanged active substance canbeinferredfromthe single-dose kinetics whenapplyingtheusualdosage schedule.At acreatinineclearance of<10 mL/min,thecalculatedsteady-stateplasmalevelsofthehydroxymetabolitesare

about4timeshigherthanin normalsubjects.However,themetabolitesareultimately clearedthroughthebile.

*Patientswith hepaticdisease:*In patientswith chronichepatitisor non- decompensated cirrhosis,the kineticsand metabolismof diclofenac arethe sameasin patients without liver disease.

5.3 Preclinical safety data

Therearenopre-clinicaldataofrelevancetotheprescriberthatareadditional to that alreadyincluded inother sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Sodium Starch Glycollate
(Sodium Starch Glycolate)
Starch
Magnesium Stearate
Instacoat EN-Super-II ENS-II-186 brown
Purified Water

6.2 Incompatibilities

Not Known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu Alu Blister pack

6.6 Special precautions for disposal

Anyunused medicinal product or waste material should be disposed of in accordancewith local requirements.

7. MARKETING AUTHORISATION HOLDER

TROIKAA PHARMACEUTICALS LTD.
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8. MARKETING AUTHORISATION NUMBER(S)

TRO/IND/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- Date of first authorization : 26December2012
- Date of renewal : 21 June 2017

10. DATE OF REVISION OF THE TEXT

28 July 2023