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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING DICLOFENAC

(57) Abstract: The present invention relates to analgesic, anti-inflammatory and antipyretic pharmaceutical formulations comprising diclofenac that shall be used in the treatment of the diseases such as mild, moderate and severe pain, arthralgia, fever, toothache, dysmenorrhea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache. Said formulations are characterized by being in effervescent form.

PHARMACEUTICAL COMPOSITIONS COMPRISING DICLOFENAC

The present invention relates to analgesic, anti-inflammatory and antipyretic pharmaceutical formulations comprising diclofenac that shall be used in the treatment of diseases such as mild, moderate and severe pain, arthralgia, fever, toothache, dysmenorrhea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache. Said formulations are characterized by being in effervescent form.

Diclofenac was first disclosed in the application numbered US3558690. In said document, it has been indicated that diclofenac has analgesic, anti-inflammatory and antipyretic impact and it is effective in the treatment of diseases such as mild, moderate and severe pain, arthralgia, fever, toothache, dysmenorrhea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache.

Diclofenac is available in the forms of 25 mg and 50 mg dragee; 75 mg/3ml ampoule; 1%, 2% and 3% gel; 100 mg capsule; 0.1% eye drop; 50 mg and 100 mg suppository; 75 mg and 100 mg sustained release tablet; 25 mg, 50 mg and 100 mg enteric-coated tablet and 100 mg retard tablet on the market. However, these dosage forms comprised in the prior art are disadvantageous for pediatric and geriatric patients and people who have swallowing difficulties. In addition, they are not preferred by most patients.

An alternative to remove this problem can be to formulate the pharmaceutical composition in suspension form. However suspension forms are not mostly preferred due to the reasons that they carry the possibility of uncontrolled dose intake, their production costs are high, they have physical and chemical instability problems, they pose problems during use and carrying phases. Although suspension forms have higher bioavailability values as compared to solid dosage forms, it is seen that they are more inconvenient than solid dosage forms when evaluated in terms of stability and shelf-life.

In the prior art, the pharmaceutical compositions comprising diclofenac have been prepared in tablet and suspension forms. However, use of tablet dosage form cause problems for those who have swallowing difficulties such as children, elderly and disabled people or for those who do not want to swallow tablets or capsules. Solution dosage forms, on the other hand, are not preferred since they complicate compliance of the patients with the treatment as they carry

the possibility of uncontrolled dose intake, have bad taste and are not user-friendly and since they have shorter shelf life than solid dosage forms due to their low stability.

When the prior art is evaluated, it has been seen that there is need for new dosage forms comprising diclofenac which have fast dissolution and impact, are user-friendly and convenient for patients who have swallowing difficulties.

The inventors have surprisingly found that the problems in the prior art can be solved by the effervescent formulations prepared according to the subject of the present invention.

Description of the Invention

The present invention relates to analgesic, anti-inflammatory and antipyretic pharmaceutical formulations comprising diclofenac and characterized by being in effervescent form that shall be used in the treatment of the diseases such as mild, moderate and severe pain, arthralgia, fever, toothache, dysmenorrhea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache.

The formulations of the present invention are characterized in that they are in the form of effervescent powder, tablet and granule which have the advantages of both tablet and suspension forms together and they remove the problems encountered in said dosage forms. Effervescent dosage forms are useful especially for patients who have swallowing difficulties.

The pharmaceutical formulations of the present invention comprise effervescent oral dosage forms comprising at least one pharmaceutically acceptable excipient in addition to diclofenac and effervescent couple or comprising only diclofenac and effervescent couple.

In one aspect, the present invention relates to effervescent oral dosage forms comprising diclofenac as the active agent, effervescent couple and at least one pharmaceutically acceptable excipient.

Diclofenac comprised in the formulations of the present invention is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof in terms of chemical structure; in amorphous form or crystalline form or a combination thereof in terms of polymorphic structure.

One characteristic feature of the effervescent formulations of the present invention is that the amount of diclofenac comprised in the formulations is in the range of 1% to 90% by weight,

preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight.

Another characteristic feature of the effervescent formulations of the present invention is that the formulations are in effervescent powder, tablet and granule forms.

The characteristic feature of the effervescent formulations of the present invention is that

- they are in effervescent powder, tablet and granule forms and
- the amount of diclofenac comprised in the formulations is in the range of 1% to 90% by weight, preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight.

The effervescent formulations of the present invention are used as dissolved in a glass of water or in another suitable liquid. At this point, it is clear that water solubility of the formulation is a very important parameter in order to provide an effective treatment and therefore bioavailability.

The inventors have found that the highest solubility in the effervescent formulations comprising diclofenac is obtained with the formulations wherein the average particle size of diclofenac is less than 50 μm in the effervescent formulations comprising diclofenac as the active agent.

According to this, one characteristic feature of the effervescent formulations of the present invention is that the formulations comprise diclofenac having an average particle size less than 50 μm as the active agent.

In another aspect, another characteristic feature of the effervescent formulations of the present invention is to comprise diclofenac having an average particle size in the range of 1 μm to 50 μm as the active agent.

In another aspect, another characteristic feature of the effervescent formulations of the present invention is to comprise diclofenac having an average particle size in the range of 1 μm to 45 μm as the active agent.

The characteristic feature of the effervescent formulations of the present invention comprising diclofenac is that

- they are in effervescent powder, tablet and granule forms
- the amount of diclofenac comprised in said formulations is in the range of 1% to 90% by weight, preferably in the range of 1% to 85% by weight, more preferably in the range of 1% to 80% by weight and
- the average particle size of diclofenac comprised in the formulations is less than 50 μm, preferably in the range of 1 μm to 50 μm and more preferably in the range of 1 μm to 45 μm.

The term ''average particle size'' used herein refers to average particle size by volume and is also shown with d_{50} in short. In this sense, the term d_{50} signifies that one half of the said substance by volume has a particle size over the value stated with d_{50} and the other half of the substance by volume has a particle size below the value stated with d_{50}.

D_{50} value can be measured with one of the known measuring devices, for instance with a device which measures particle distribution by laser diffraction (for instance, Malvern Mastersizer etc.).

Another characteristic feature of the effervescent formulations of the present invention is that the formulations comprise at least one pharmaceutically acceptable excipient along with diclofenac and effervescent couple.

The excipients that can be comprised in the effervescent formulations of the present invention can be selected from a group comprising binders, disintegrants, viscosity enhancing compounds, filling agents, drying agents, surfactants, stabilizing agents, oiling agents, lubricants, diluents, glidants, wetting agents, oiling agents, pH regulators, effervescent acids, effervescent bases, gelling agents, flavouring agent, sweeteners, taste regulating agents, emulsifying agents, antifoaming agents, antioxidants, preservative agents, solvent or solvent mixtures, colouring agents and complexing agents or combinations thereof.

The disintegrant that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch glycolate.

The diluent that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

The oiling agent that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.

The binder that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch.

The effervescent acids that can be used in the effervescent formulations of the present invention comprising diclofenac are selected from a group comprising organic acids such as citric acid and acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or pharmaceutically acceptable hydrates, anhydrates and similar forms or combinations thereof.

The effervescent bases that can be comprised in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising alkaline or alkaline earth metal carbonates or bicarbonates or combinations thereof.

Potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate and sodium bicarbonate or combinations thereof can be given as examples of the effervescent bases which are preferred in the formulations of the present invention.

The effervescent formulations of the present invention comprising diclofenac comprise an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and effervescent base in the range of 10% to 95%, preferably in the range of 15% to 95%, more preferably in the range of 20% to 95% in proportion to total weight of formulation.

According to this, the term ''effervescent couple'' refers to mixture of at least one effervescent acid and at least one effervescent base. Both or either of these agents can be in

combination form of different types in the mixture of effervescent couple. For instance, an effervescent couple comprising two different effervescent acids and one effervescent base or two different effervescent acids and two different effervescent bases can be used.

The ratio of at least one pharmaceutically acceptable effervescent acid to the effervescent base comprised in the effervescent formulations of the present invention comprising diclofenac is in the range of 0.1 to 10 by weight.

The pH regulating agent that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from citrate, phosphate, carbonate tartrate, fumarate, acetate and amino acid salts.

The surfactant that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from the agents comprising sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and so forth.

The stabilizing agents that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

The sweetener and/or taste regulating agent that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharin, saccharin sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride.

The flavouring agent that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from flavours comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and so forth.

The lubricants that can be used in the effervescent formulations of the present invention comprising diclofenac can be selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate or combinations thereof.

The excipients that can be used in the effervescent formulations of the present invention comprising diclofenac are preferably selected from a group comprising binders, disintegrants, filling agents, surfactants, stabilizing agents, oiling agents, lubricants, diluents, glidants,

effervescent acids, effervescent bases, flavouring agents, sweeteners, solvent or solvent mixtures or combinations thereof.

The effervescent formulations of the present invention comprising diclofenac can optionally comprise a second active agent in addition to diclofenac. The second active agent can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antidiabetic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

In the case that two active agents are comprised in the same formulation, the pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to diclofenac can be prepared in any dosage forms such as effervescent tablet, effervescent granule, effervescent dry powder; in the case that the two active agents are comprised in different formulations but in the same dosage form, the pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to diclofenac can be prepared in the dosage forms such as layered tablet, capsule; in the case that the two active agents are comprised in different formulations and in different dosage forms, the pharmaceutical formulations prepared according to the process of the present invention and comprising a second active agent in addition to diclofenac can be prepared in a treatment package form wherein diclofenac is in any dosage forms of effervescent tablet, effervescent granule, effervescent dry powder; the second active agent, on the other hand, is in any solid dosage forms such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enteric coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

Preparation method of the formulations of the present invention comprises the steps of formulating the active agent with the suitable excipient compound and forming the said formulation in the required shape.

Any production method in the prior art can be used to formulate the formulations of the present invention; wet granulation, dry granulation and dry blending methods can be listed among these production methods.

More specifically, the formulations of the present invention can be produced according to any production methods given below;

1. Mixing the active agent diclofenac and, if available, the second active agent with at least one pharmaceutically acceptable excipient homogeneously and, if required, adding at least one of the abovementioned excipients; optionally treating the mixture with at least one pharmaceutically acceptable lubricant; forming the powder mixture obtained in a desired shape,
2. Optionally wet-granulating the mixture, which is obtained by mixing the active agent diclofenac and, if available, the second active agent with at least one pharmaceutically acceptable excipient homogeneously, with the granulation solution comprising at least one excipient; drying the granules obtained, optionally adding at least one pharmaceutically acceptable excipient into the dry granules and forming the granules obtained in a desired shape,
3. Optionally wet-granulating at least one abovementioned excipient with the granulation solution comprising at least one excipient; drying the granules obtained; adding diclofenac, and, if available, the second active agent and optionally at least one excipient into the dry granules and mixing; forming the granules obtained in a desired shape,
4. Dry-granulating the mixture, which is obtained by adding the active agent diclofenac and, if available, the second active agent and at least one of the abovementioned excipients, and forming the granules obtained in a desired shape.

The formulations of the present invention can be

- compressed in tablet form,
- filled into sachets

in order to obtain the dosage form required after prepared according to any methods given.

The effervescent formulations of the present invention are preferably in tablet form.

The inventors have seen that in the case that these effervescent formulations are prepared in tablet dosage form, water solubility of the formulations is affected by tablet compression force.

According to this, compressing the formulations produced according to any abovementioned methods in the prior art in tablet form under a tablet compression force in the range of 3 kN to 50 kN, preferably in the range of 4 kN to 45 kN, more preferably in the range of 4 kN to 40 kN cause a positive improvement in solubility of the end product.

The characteristic feature of the effervescent formulations of the present invention comprising diclofenac is that

- the said formulations are in effervescent form and

tablet compression force implemented during compressing said formulations into tablet form is in the range of 3 kN to 50 kN, preferably in the range of 4 kN to 45 kN, more preferably in the range of 4 kN to 40 kN.

The pharmaceutical formulations of the present invention have analgesic, anti-inflammatory and antipyretic effects and they can be used in the treatment of diseases such as mild, moderate and severe pain, arthralgia, fever, toothache, dysmenorrhea, toothache, myalgia, osteoarthritis, rheumatoid arthritis, backache.

The examples below are given to explain the pharmaceutical compositions of the present invention and preparation methods thereof; yet, the subject of the present invention cannot be limited to these examples.

EXAMPLES

Example I.

Component	% of amount in unit dose
Diclofenac	3
Effervescent Acid	45
Effervescent Base	28
Lubricant	4.5
Sweetener	2.5
Other excipients	17
Total	100.0

The effervescent formulation given above is produced according to any methods in the prior art explained in detail in the description; and the formulation is presented for use in the desired dosage form.

CLAIMS

1. A pharmaceutical formulation comprising diclofenac, characterized in that said formulation is in effervescent form.
2. The formulation according to claim 1, characterized in that diclofenac is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof; in amorphous form or crystalline form or a combination thereof in terms of polymorphic structure.
3. The formulation according to claims 1-2, characterized in that diclofenac comprised in the formulation is in the range of 1% to 90% by weight.
4. The formulation according to claims 1-3, characterized in that the amount of diclofenac comprised in the formulation is in the range of 1% to 85% by weight.
5. The formulation according to claims 1-4, characterized in that the amount of diclofenac comprised in the formulation is in the range of 1% to 80% by weight.
6. The formulation according to any preceding claims, characterized in that said formulation is in effervescent powder, tablet and granule forms.
7. The formulation according to any preceding claims, characterized in that the average particle size of diclofenac comprised in the formulation is less than 50 μm.
8. The formulation according to claim 7, characterized in that the average particle size of diclofenac comprised in the formulation is in the range of 1 μm to 50 μm.
9. The formulation according to claims 7-8, characterized in that the average particle size of diclofenac comprised in the formulation is in the range of 1 μm to 45 μm.
10. The formulation according to any preceding claims, characterized in that said formulation comprises at least one pharmaceutically acceptable excipient.
11. The formulation according to claim 10, characterized in that the excipients that can be comprised in the formulation are selected from binders, disintegrants, viscosity enhancing components, filling agents, drying agents, surfactants, stabilizing agents, oiling agents, lubricants, diluents, glidants, wetting agents, oiling agents, pH regulating agents, effervescent acids, effervescent bases, gelling agents, flavouring agent, sweeteners, taste regulating agents, emulsifying agents, antifoaming agents, antioxidants, preservatives, solvent or solvent mixtures, colouring agents and complexing agents or combinations thereof.
12. The formulation according to claim 11, characterized in that the excipients that can be comprised in the formulation are selected from a group comprising binders,

disintegrants, filling agents, surfactants, stabilizing agents, oiling agents, lubricants, diluents, glidants, effervescent acids, effervescent bases, flavouring agents, sweeteners, solvent or solvent mixtures, or combinations thereof.

13. The formulation according to claim 12, characterized in that the effervescent acids that can be comprised in the formulation are selected from a group comprising organic acids such as citric acid and acetic acid, tartaric acid, fumaric acid, adipic acid, malic acid or pharmaceutically acceptable hydrates, anhydrates and similar forms or combinations thereof.

14. The formulation according to claim 12, characterized in that effervescent bases that can be comprised in the formulation are selected from a group comprising alkaline or earth alkaline metal carbonates or bicarbonates or combinations thereof.

15. The formulation according to claim 12, characterized in that effervescent bases that can be comprised in the formulation are selected from a group comprising potassium carbonate, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium carbonate and sodium bicarbonate or combinations thereof.

16. The formulation according to claims 12-15, characterized in that said formulation comprises an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and at least one effervescent base in the range of 10% to 95% in proportion to total weight of formulation.

17. The formulation according to claim 16, characterized in that said formulation comprises an effervescent couple composed of at least one pharmaceutically acceptable effervescent acid and at least one effervescent base in the range of 15% to 95% in proportion to total weight of formulation.

18. The formulation according to claims 16-17, characterized in that said formulation comprises at least one pharmaceutically acceptable effervescent acid and at least one effervescent base in the range of 20% to 95% in proportion to total weight of formulation.

19. The formulation according to claims 16-18, characterized in that the ratio of at least one pharmaceutically acceptable effervescent acid to at least one effervescent base comprised in the formulation is in the range of 0.1 to 10.

20. A method for production of a formulation according to any preceding claims, characterized in that said method comprises the steps of wet granulation, dry granulation, dry blending or combinations thereof.

21. A tablet form comprising diclofenac as the active agent, characterized in that said tablet form
    a. is in effervescent form
    b. comprises diclofenac in the range of 1% to 90% and
    c. is compressed with a compression force in the range of 3 kN to 50 kN.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000037

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 217 598 A (CIBA GEIGY [CH]) 1 November 1989 (1989-11-01) the whole document claims 1-12; examples 1-9	1-21
X	US 5 211 957 A (HAGEMANN RUTH [CH] ET AL) 18 May 1993 (1993-05-18) the whole document claims 1-4; examples 1-9	1-21
X	DE 44 03 943 A1 (HEXAL PHARMA GMBH [DE]) 10 August 1995 (1995-08-10) the whole document claims 1-11; examples 1-4	1-21

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000037

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/063199 A1 (BAYER HEALTHCARE AG [DE]; WIEHL WOLFGANG [DE]; LOOSE IRENE [DE]; BUELL) 14 July 2005 (2005-07-14) the whole document claims 1-23; examples 1-7	1-21
X	US 2004/258740 A1 (THOMPSON WILLIAM ALEJANDRO [US]) 23 December 2004 (2004-12-23) the whole document claims 1-20; examples 1-6	1-21
A	BOWEN P: "Particle Size Distribution Measurement from Millimeters to Nanometers and from Rods to Platelets", JOURNAL OF DISPERSION SCIENCE AND TECHNOLOGY, TAYLOR AND FRANCIS GROUP, NEW YORK, NY, US, vol. 23, no. 5, 1 January 2002 (2002-01-01), pages 631-662, XP009102859, ISSN: 0193-2691, DOI: 10.1081/DIS-120015368 the whole document figures 9,24,27; tables 4,6	7-9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/TR2013/000037

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