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(71) **Applicant**: **SANOVEL ILAC SANAYI VE TICARET A.S.** [TR/TR]; Balabandere Cad. Ilac Sanayi Yolu No: 14 Istinye, Sariyer, 34460 Istanbul (TR).

(72) **Inventors**: **CIFTER, Ümit**; Sanovel Ilac Sanayi Ve Ticaret A.S., Balabandere Cad. Ilac Sanayi Yolu No: 14 Istinye, Sariyer, 34460 Istanbul (TR). **TÜRKYILMAZ, Ali**; Sanovel Ilac Sanayi Ve Ticaret A.S., Balabandere Cad. Ilac Sanayi Yolu No: 14 Istinye, 34460 Istanbul (TR). **YELKEN, Gülay**; Sanovel Ilac Sanayi Ve Ticaret A.S., Balabandere Cad. Ilac Sanayi Yolu No: 14 Istinye, 34460 Istanbul (TR).

(74) **Agent**: **SEVINC, Erkan**; Istanbul Patent A.S., Plaza-33, Buyukdere cad. 33/16 Sisli, 34381 Istanbul (TR).

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(54) **Title**: PHARMACEUTICAL COMBINATIONS OF CONTROLLED RELEASE FLURBIPROFEN AND DIACEREIN

(57) **Abstract**: The present invention relates to a pharmaceutical combination of flurbiprofen or a pharmaceutically acceptable salt thereof and diacerein or a pharmaceutically acceptable salt thereof.

PHARMACEUTICAL COMBINATIONS OF CONTROLLED RELEASE FLURBIPROFEN AND DIACEREIN

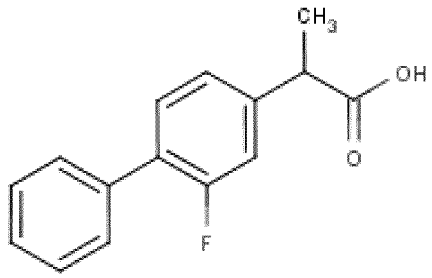
Technical Field

The present invention relates to a pharmaceutical combination of flurbiprofen or a pharmaceutically acceptable salt thereof and diacerein or a pharmaceutically acceptable salt thereof.

Particularly, the pharmaceutical combination comprising: a controlled release layer comprising flurbiprofen or a pharmaceutically acceptable salt thereof and an immediate release layer comprising diacerein or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

Background of the invention

Flurbiprofen is a propionic acid derivative which is an NSAID (non-steroidal anti-inflammatory drug), having analgesic and anti-inflammatory activities. Its chemical structure is illustrated with Formula 1 given below.



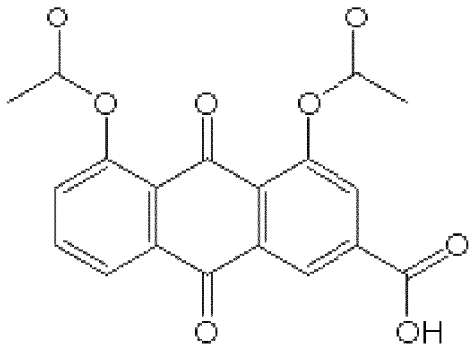
Formula 1

Flurbiprofen is used for alleviating pain in muscle-skeleton system and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft tissue injuries such as sprains and strains, in postoperative cases, and in painful severe menstruation and migraine. It is in the market under the brandname of ANSAID® in strength of 50, 100, 200 and 300 mg. It is recommended 2, 3 or 4 times a day dose.

Multiple daily dosing leads serious side effects which decrease the patient's quality of life.

The most frequent side effects of immediate release flurbiprofen are including gastrointestinal (GI) adverse effects such as inflammation, spontaneous gastric bleeding, ulceration and perforation of the stomach, which can be life threatening. Another disadvantage of flurbiprofen is that it is practically insoluble in water. This makes it difficult to prepare controlled release formulations.

Another molecule that can be used especially in the treatment of osteoarthritis is diacerein disclosed in the patent US4244968A. It is interleukin-1 inhibitor having anthraquinone structure and chemical structure thereof is shown in Formula 2.



Formula 2

Diacerein is also available in the market under the brand names Artrodar® and Rexena® and it is in the form of capsule in the strength of 50 mg for once daily use. It is known that diacerein has a different mechanism of action than the other NSAIDs. It works by blocking the actions of interleukin-1 beta, a protein involved in the inflammation process

While combining more than one molecule in one dosage form is increasing the patients' quality of life, many challenges also occur such as(a) the physicochemical compatibility between the different active agents and/or between the active agents and the excipients used; and (b) the therapeutical compatibility between the two active agents regarding their pharmacokinetic and/or pharmaceutical properties in order that the posology of the combined formulation allows to obtain safe and efficient plasma levels of both pharmacological agents.

Use of flurbiprofen and diacerein in combination may cause some, particularly gastrointestinal, side effects. Flurbiprofen shows burning sensation in the

gastrointestinal system and diacerein shows gastrointestinal side effect of diarrhea as well. Moreover, the use of diacerien with flurbiprofen can cause additional effects. Avoiding these systemic adverse effects of flurbiprofen and diacerein is very important for the patient.

Therefore, in prior art, flurbiprofen and diacerein has been used in combination. However, none of them comprises controlled release flurbiprofen and diacerein in the same oral dosage form.

In this invention, a controlled release layer has been specifically formulated as to contain flurbiprofen and release slowly it over in a desired period of time, until the next dosage is administered. The formulation of this present invention also comprises an immediate release layer comprising diacerein which has a different mechanism of action in the treatment of osteoarthritis. As a result, an effective and safe administration of flurbiprofen and diacerein combination has been achieved for the patients' compliance.

Background of the Invention

The main embodiment of this present invention is a pharmaceutical combination comprising: (1) a controlled release layer comprising flurbiprofen or a pharmaceutically acceptable salt thereof, (2) an immediate release layer comprising diacerein or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

In one embodiment, the pharmaceutical combination is in the form of multilayer tablet. In order to combine two different molecules with two different release profile in one dosage form, in this invention two layers that have different release profiles have been designed; a controlled release layer, an immediate release layer and optionally an intermediate layer.

In one embodiment, flurbiprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 20-80 % by weight of controlled release layer and the diacerein or a pharmaceutically acceptable salt thereof is present in an amount of between 5 – 90% by weight of immediate release layer.

In one embodiment, the ratio of flurbiprofen to diacerein is between 10:1 to 1:1 (w/w), preferably 6:1 to 1:1 (w/w) and more preferably 6:1 to 4:1 (w/w). To achieve different desired dose of active agents, these ratios have been used in separate layers.

In one embodiment, the pharmaceutical combination further comprises a release rate controlling agent in controlled release layer comprising flurbiprofen. As used herein, the term "release rate controlling agent" is defined as the pharmaceutical ingredient that provides controlled release, modified release, retarded release, slow release, sustained release, prolonged release, zero point order release or extended release.

The term "controlled release" is defined as reaching desired plasma levels of an active agent of interest throughout a determined period of time, and providing the drug release at a uniform and constant rate. In this present invention, the aim of using release rate controlling agent was to improve dissolution characteristics while achieving a desired controlled release flurbiprofen profile.

In one embodiment, release rate controlling agent has been used in a specific ratio and it has been surprisingly found that controlled release of flurbiprofen has been achieved without affecting diacerein release profile in immediate release layer. In this the pharmaceutical combination of this present invention, the ratio of flurbiprofen to release rate controlling agent is between 1:2 to 16:1 (w/w), preferably 1:2 to 10:1 (w/w), more preferably it is 1:2 to 5:1 (w/w) in controlled release layer.

According to this embodiment, release rate controlling agent is selected from the group comprising polyvinyl acetate, polyvinylpyrrolidone,HPMC (hydroxyl propyl methylcellulose), hydroxyethyl methylcellulose, hydroxypropyl cellulose, hydroxypropylethylcellulose, ethylcellulose, methacrylicacid – ethyl acrylate copolymer, polymethylmetacrylate or copolymers, polyvinyl alcohol, glycerylbehenate, polyethylene oxide, polyethylene glycol, cellulose acetate, vinyl acetate/crotonic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, copolymer of acrylic or methacrylic acid esters, polyoxyethylene -alkyl ethers, lambda (λ) carrageenan, ethylcellulosepolymers or copolymers, polymethacrylates or copolymers, natural gums such as xanthan gum, surfactants as cetostearyl alcohol, cethyl alcohol or mixtures thereof. Preferably, it is the mixture of polyvinyl acetate and polyvinyl pyrrolidone.

In this invention, the mixture of polyvinyl acetate and polyvinyl pyrrolidone comprised of 80 % of polyvinyl acetate and 19 % of polyvinyl pyrrolidone by weight of total mixture.

It is difficult to develop a tablet formulation comprising flurbiprofen has low solubility in terms of the process. Herein, the mixture of polyvinyl acetate and polyvinyl pyrrolidone is used to further improve the process conditions by increasing the flurbiprofen solubility, as well as being controlled release agent.

According to this embodiment, the mixture of polyvinyl acetate and polyvinyl pyrrolidone has been used in a specific ratio and it has been found that controlled release of flurbiprofen has been achieved without affecting diacerein release profile in immediate release layer. In this pharmaceutical combination of this present invention, the ratio of flurbiprofen to the mixture of polyvinyl acetate and polyvinyl pyrrolidone is between 1:2 to 16:1 (w/w), preferably 1:2 to 10:1 (w/w), more preferably it is 1:2 to 5:1 (w/w) in controlled release layer.

According to this embodiment, binder is selected from the group comprising starch, polyvinylpyrrolidone (povidone), pregelatinized starch, lactose, polymethacrylate, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxyethyl cellulose, sodium carboxy methyl cellulose (NaCMC), carboxymethyl cellulose calcium, ethyl cellulose, polyethylene oxide, gelatin, xanthan gum, guar gum, alginate, carrageenan, pectin, carbomer, cellulose acetate phthalate, hydroxy propyl starch, polaxomer, polyethylene glycol and mixtures thereof. Preferably, it is starch.

In one embodiment, the pharmaceutical combination **further** comprises starch.

According to one embodiment, due to starch used as a binder in the formulation, hardness of the tablet has been improved, layers adhere to each other and robust multilayer tablet with desired dissolution has been achieved.

In one embodiment, the pharmaceutical combination is in the form of trilayer tablet.

In one embodiment, the pharmaceutical combination is in the form of bilayer tablet.

In one embodiment, the pharmaceutical combination is in the form of coated tablet.

In one embodiment, the pharmaceutical combination is in the form of tablet in tablet.

In one embodiment, the pharmaceutical combination is in the form of inlay tablet.

Coating material may be selected from the group comprising methylacrylate copolymer (Eudragit EPO) and other polymethylmetacrylate copolymers (Eudragit), polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat IR), polyvinyl alcohol or copolymers or mixtures thereof (Opadry AMB), Ethylcellulose Dispersions (Surelease), Kerry-HPC, polyethylene glycol, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer(PVP-VA), and all kinds of OpadryTM such as Opadry pink II, as well as pigments, dyes, titanium dioxide and iron oxide.

Suitable diluents may include but not limited to microcrystalline cellulose, lactose, corn starch, modified corn starch, calcium phosphate, sugar, dextrose, mannitol, sorbitol, starch, pregelatinized starch and mixtures thereof.

Suitable disintegrants may include but not limited to microcrystalline cellulose, croscarmellose sodium, xylitol, polyplasdone (1-ethenylpyrrolidin-2-one), crospovidone, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate or mixtures thereof.

Suitable glidants may include but not limited to colloidal silicon dioxide, silicon dioxide, talc, magnesium trisilicate, starch or silicon hydrogel or mixtures thereof.

Lubricants according to the present invention include, but not limited to magnesium stearate, sodium stearyl fumarate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium chloride benzoate and acetate, sodium or magnesium lauryl sulfate or mixtures thereof.

Suitable plasticizers may include but not limited to triethyl citrate, triacetin, citric acid esters, phthalic acid esters, dibutylsebacate, cetyl alcohol, polyethylene glycol, polysorbate or mixtures thereof.

Suitable surfactants may include but not limited to dioctylsulfosuccinate, polysorbates and polyoxyethylene alkyl esters and ethers thereof, glycerylmonolauratesaponins, sorbitanlaurate, sodium lauryl sulfate, magnesium lauryl sulfate or mixtures thereof.

Suitable preservatives may include but not limited to methyl paraben, propyl paraben and salts thereof (e.g. sodium or potassium salts), sodium benzoate, citric acid, benzoic acid, butylatedhydroxytoluene and butylatedhydroxyanisole or mixtures thereof.

Example 1 - Trilayer Tablet

	Ingredients	Amount %
Controlled Release Layer	flurbiprofen	20 - 80%
	starch	5 – 90 %
	microcrystalline cellulose	5 – 90 %
	croscarmellose sodium	0.5 - 25%
	Polyvinyl Acetate/ Polyvinylpyrrolidone (Kollidon SR)	5 – 40 %
	colloidal silicon dioxide	0.1 – 10 %
	magnesium stearate	0.1 – 10 %
İntermediate layer	sodium carboxymethylcellulose	0.1 - 20 %
	polyvinylpyrrolidone	0.1 – 25 %
	microcrystalline cellulose	5 – 90 %
	colloidal silicon dioxide	0.1 – 10 %
	magnesium stearate	0.1 – 10 %
Immediate release layer	diacerein	5 – 90 %
	starch	5 – 90 %
	croscarmellose sodium	0.5 - 25%
	povidone	3 – 20 %
	colloidal silicon dioxide	0.1 – 5 %
	sodium stearylfumarate	0.1 – 10 %

The process of the formulation is carried out as follows:

Controlled release layer: Flurbiprofen, a portion of microcrystalline cellulose, starch, croscarmellose sodium and polyvinyl acetate/ polyvinylpyrrolidoneare mixed; colloidal silicon dioxide and rest of the microcrystalline cellulose are sieved, added into the

mixture obtained and mixed. Then,tablets are compressed into bricks, crushed and sieved. Magnesium stearate is added into the mixture obtained and mixed.

Immediate release layer: Diacerein, a portion of starch, croscarmellose sodium and povidone are mixed. Colloidal silicon dioxide and rest of the starch are sieved, added into the mixture obtained and mixed. Then, Sodium stearylfumarate is added into this mixture and mixed.

Intermediate layer: Sodium carboxymethyl cellulose, polyvinylpyrrolidone and a portion of microcrystalline cellulose are mixed. Rest of the microcrystalline cellulose and colloidal silicon dioxide are sieved and added into the mixture obtained and mixed. Then, magnesium stearate is added into the mixture obtained and mixed.

Homogeneous mixtures obtained for each layer are compressed so as to obtain a trilayer tablet with the barrier layer provided in the middle thereof.

Example 2 - Bilayer Tablet

	Ingredients	**amount (%)**
Controlled Release Layer	flurbiprofen	20 - 80%
	Polyvinyl Acetate/ Polyvinylpyrrolidone (Kollidon SR)	5 - 40%
	polyethylene glycol	0.1 – 2 %
	microcrystalline cellulose	5 – 90 %
	starch	5 – 90 %
	magnesium stearate	0.1 – 10 %
Immediate Release Layer	diacerein	5 - 90 %
	croscarmellose sodium	0.5 - 25%
	polyvinylpyrrolidone	0.1 – 25 %
	microcrystalline cellulose	5 – 90 %
	starch	5 – 90 %
	colloidal silicon dioxide	0.1 – 5 %
	magnesium stearate	0.1 – 10 %

The process of the formulation is carried out as follows:

Controlled release layer: polyethylene glycol is dissolved in water and half of polyvinyl acetate/ polyvinylpyrrolidone is added and mixed together (mixturei). Flurbiprofen and microcrystalline cellulose is added to high-shear mixture, then mixture i is added to this mixture and the mixture is granulated while the mixer is open. Then, granules are dried in fluid bed dryer and sieved. The sieved granules obtained are coated with the rest of the polyvinyl acetate/ polyvinylpyrrolidonein fluid bed dryer, finally starch and magnesium stearate are added to this granules as an external phase.

Immediate release layer: diacerein,microcrystalline cellulose, starch and half of the croscarmellose sodium are mixed together, then they are granulated with the water-solution of polyvinylpyrrolidone. Obtained granules are then sieved and dried in oven. The dried granules are also sieved and colloidal silicon dioxide, magnesium stearate and rest of the croscarmellose sodium are added as an external phase.

Finally, compression step is performed to form the bilayer tablets

Example 3 - Bilayer Tablet

	Ingredients	**amount (%)**
Controlled Release Layer	Flurbiprofen	20 - 80%
	Neutral pellet	5 - 25%
	Polyvinyl Acetate/ Polyvinylpyrrolidone (Kollidon SR)	5 - 40%
	triethyl citrate	0.1 – 5 %
	colloidal silicon dioxide	0.1 – 10 %
	polyethylene glycol	0.1 – 2 %
	microcrystalline cellulose	5 – 90 %
	magnesium stearate	0.1 – 10 %
Immediate Release Layer	diacerein or salts thereof	5 - 90 %
	croscarmellose sodium	0.5 - 25%
	polyvinylpyrrolidone	0.1 – 25 %
	microcrystalline cellulose	5 – 90 %
	starch	5 – 90 %
	colloidal silicon dioxide	0.1 – 5 %
	magnesium stearate	0.1 – 10 %

The process of the formulation is carried out as follows:

Controlled release layer: Water is added to a tank which comprise a mechanic stirrer and a homogenizer (mixture i), and triethly citrate is added to this tank and it is mixed with the mechanic stirrer (mixture ii). Flurbiprofen is added to mixture ii while the homogenizer is open to obtain the mixture iii. Polyvinyl acetate/ polyvinylpyrrolidoneis added to mixture III while the homogenizer is closed and it is mixed until a homogenous mixture is obtained and no bubles remain (mixture iv). Then, neutral pellets are added to fluid bed dryer and the mixture iv is coated on the pellets with spraying. After the coating step, colloidal silicon dioxide is added on the coated pellets and coated pellets are sieved. Sieving is important in this step to prevent the coated pellets from sticking to each other. Finally, polyethylene glycol, microcrystalline cellulose and magnesium stearate are added to these granules as an external layer.

Immediate release layer: diacerein,microcrystalline cellulose, starch and half of the croscarmellose sodium are mixed together, then they are granulated with the water-solution of polyvinylpyrrolidone. Obtained granules are then sieved and dried in oven. Dried granules are also sieved and colloidal silicon dioxide, magnesium stearate and rest of the croscarmellose sodium are added as an external layer.

Finally, compression step is performed to form the bilayer tablets.

Example 4 - Coated Tablet

	Ingredients	**amount (%)**
Controlled Release Layer	Flurbiprofen	20 – 80%
	Polyvinyl Acetate/ Polyvinylpyrrolidone (Kollidon SR)	5 – 40%
	colloidal silicon dioxide	0.1 – 10%
	magnesium stearate	0.1 – 10%
Immediate Release Layer	diacerein or salts thereof	5 – 90%
	methylacrylate copolymer (Eudragit EPO)	0.5 – 40%
	starch	5 – 90 %
	Poliethylen glycol (PEG 8000)	1 – 5%
	Talc	1 – 20%

The process of the formulation is carried out as follows:

Controlled release layer: Flurbiprofen, polyvinyl Acetate/ polyvinylpyrrolidone , colloidal silicon dioxide and magnesium stearate are mixed and granulated with high shear granulator or they are obtained from extruder to become pellets by spheronizer and after dried by fluid bed drier or dried in oven, they are sieved and pressed or matrix tabletsare pressed by direct compression.

Immediate release layer: Water is used for the preparation of film coating mixture.Diacereinand Eudragit EPO are dissolved in water and PEG, starch and then talc is added to this mixture and it is mixed until having a homogenous mixture.The pressed controlled release flurbiprofen tablets are coated with this coating suspension.These coated tablets, preferably are coated by a coating material including conventional coating polymers like Opadry®.

CLAIMS

1. A pharmaceutical combination comprising: (1) a controlled release layer comprising flurbiprofen or a pharmaceutically acceptable salt thereof and (2) an immediate release layer comprising diacerein or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

2. The pharmaceutical combination according to claim 1, wherein the flurbiprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 20-80 % by weight of controlled release layer and the diacerein or a pharmaceutically acceptable salt thereof is present in an amount of between 5 – 90% by weight of immediate release layer.

3. The pharmaceutical combination according to claim 2, wherein the ratio of flurbiprofen to diacerein is between 10:1 to 1:1 (w/w), preferably 6:1 to 1:1 (w/w) and more preferably 6:1 to 4:1 (w/w)

4. The pharmaceutical combination according to any preceding claims, further comprising a release rate controlling agent.

5. The pharmaceutical combination according to any preceding claims, wherein the ratio of flurbiprofen to release rate controlling agent is between 1:2 to 16:1 (w/w), preferably 1:2 to 10:1 (w/w), more preferably it is 1:2 to 5:1 (w/w) in controlled release layer.

6. The pharmaceutical combination according to any preceding claims, wherein the release rate controlling agent is selected from the group comprising polyvinyl acetate, polyvinylpyrrolidone, HPMC (hydroxyl propyl methylcellulose), hydroxyethyl methylcellulose, hydroxypropyl cellulose, hydroxypropylethylcellulose, ethylcellulose, methacrylic acid – ethyl acrylate copolymer, polymethylmetacrylate or copolymers, polyvinyl alcohol, glycerylbehenate, polyethylene oxide, polyethylene glycol, cellulose acetate, vinyl acetate/crotonic acid copolymers, maleic anhydride/methyl vinyl ether copolymers, copolymer of acrylic or methacrylic acid esters, polyoxyethylene - alkyl ethers, lambda (λ) carrageenan, ethylcellulose polymers or copolymers, polymethacrylates or copolymers, natural gums such as xanthan gum,

surfactants as cetostearyl alcohol, cethyl alcohol or mixtures thereof. Preferably, it is the mixture of polyvinyl acetate and polyvinyl pyrrolidone.

7. The pharmaceutical combination according to any preceding claims, wherein the ratio of flurbiprofen to the mixture of polyvinyl acetate and polyvinyl pyrrolidone is between 1:2 to 16:1 (w/w), preferably 1:2 to 10:1 (w/w), more preferably it is 1:2 to 5:1 (w/w) in controlled release layer.

8. The pharmaceutical combination according to any preceding claims, wherein the formulation further comprising starch.

9. The pharmaceutical combination according to any preceding claims, the pharmaceutical combination is in the form of multilayer tablet.

10. The pharmaceutical combination according to any preceding claims, wherein the formulation is in the form of trilayer tablet.

11. The pharmaceutical combination according to any preceding claims, wherein the formulation is in the form of bilayer tablet.

12. The pharmaceutical combination according to any preceding claims, wherein the formulation is in the form of coated tablet.

13. The pharmaceutical combination according to any preceding claims, wherein the formulation is in the form of tablet in tablet.

14. The pharmaceutical combination according to any preceding claims, wherein the formulation is in the form of inlay tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/062955

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/24 A61K31/192 A61K31/194
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.
A	EP 2 074 990 A1 (SANOVEL ILAC SANAYI VE TICARET [TR]) 1 July 2009 (2009-07-01) claim 1; examples 1-4	1-14
A	WO 2009/040702 A2 (WOCKHARDT RESEARCH CENTER [IN]; DABRE RAHUL [IN]; JAIN GIRISH KUAMR [I) 2 April 2009 (2009-04-02) page 4; claims 1,14, 45	1-14
A	WO 2013/095319 A2 (SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI [TR]) 27 June 2013 (2013-06-27) claim 1; examples 1,2	1-14
A	WO 2013/100882 A2 (SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI [TR]) 4 July 2013 (2013-07-04) claim 1; examples 1-3	1-14

☐ Further documents are listed in the continuation of Box C.

☒ 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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"O" document referring to an oral disclosure, use, exhibition or other means

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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kardas-Llorens, Eyüp

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/062955

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