Title: DOSAGE FORM COMPRISING ENZALUTAMIDE

Dissolution of Enzalutamide Formulations
Conditions: 900 ml, 0.1N HCl; pH 1.2; 37°C, 50 rpm paddle (USP app. II)

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Example 1

Refer to Example 0

Refer to Example 5

Refer to Example 1

Abstract: The present invention relates to dosage forms comprising enzalutamide, wherein the enzalutamide is present in a disolved form. Further, the invention relates to the use of a solvent having a specific HLB-value for producing a water/oil emulsion of an API having water-solubility of 1·10^(-5) mg/ml to 1·10^(-2) mg/ml.
Dosage Form Comprising Enzalutamide

Background of the Invention

The present invention relates to dosage forms comprising enzalutamide, wherein the enzalutamide is present in a dissolved form. Further, the invention relates to the use of a solvent having a specific HLB-value for producing a water/oil emulsion of an active pharmaceutical ingredient (API) having a water-solubility of $1 \times 10^{-3} \text{mg/ml}$ to $1 \times 10^{-2} \text{mg/ml}$.

Prostate cancer is a common cancer in men, especially in the US and in Europe. Prostate cancer is reported to grow slowly and can, if detected in an early stadium, be cured by the radical removal of the prostate. However, if not detected early prostate cancer can progress and result in an aggressive prostate cancer and the cancer cells may metastasize to other parts of the body and thus affect vitally important other organs, such the lymph nodes, lungs, bones and the gastrointestinal tract.

A possible handling of the disease depends on several individual conditions, such as age, general health, the extent of the cancer and possible metastasis. Thus, the decision whether or not to treat localized prostate cancer with a curative intent is a personal patient trade-off between the expected beneficial and harmful effects in terms of patient survival and the maintenance of a certain quality of life.

Enzalutamide is marketed as XTANDI® and reported to be effective in the treatment of prostate cancer. According to the FDA, XTANDI® is a liquid-filled soft gelatine capsule for oral administration comprising enzalutamide. The dosage form is reported to be used for the treatment of patients with metastatic castration-resistant prostate cancer. The recommended dose of XTANDI® is 160 mg, which should be administered orally once daily in the form of four capsules each containing 40 mg of active pharmaceutical ingredient, wherein the administration of XTANDI® is reported to be independent of food uptake. Each capsule contains
40 mg of enzalutamide as a solution, wherein the active pharmaceutical ingredient is dissolved in the solvent Labrasol®. The solvent Labrasol® is reported to consist of caprylocaproyl polyoxylglycerides.

However, the above-mentioned composition comprising enzalutamide shows a dissolution behaviour at acidic conditions, especially under simulated gastric fluid which appears to be incomplete. In particular, the API does not remain dissolved but seems to precipitate.

A further disadvantage is the recommended dose of 160 mg orally once daily, since this is related to an administration of four capsules once daily. Further, these capsules are reported to be very big due to the great amount of Labrasol® necessary to keep the active pharmaceutical ingredient in solution. Due to its big size (capsule size 12) and the high number of capsules that has to be taken, this dosage form is difficult to swallow, in particular for older men, resulting in a poor patient compliance, especially in said important patient group.

Hence, it was an object of the present invention to overcome the above problems.

Thus, it is an object of the present invention to provide a dosage form showing a superior dissolution and/or bioavailability.

Additionally, it was an object of the invention to provide an effective amount of enzalutamide in a dosage form having a suitable size and/or allowing to reduce the number of administered units such that the patient compliance can be improved.

Summary of the Invention

According to the present invention, the above objectives are achieved by a specific dosage form comprising enzalutamide in a dissolved form, a first solvent and a second solvent and optionally an oily component. Furthermore, the above drawbacks can be avoided by the use of a solvent having an HLB of 1 to 20 for
producing a water/oil emulsion of an API like enzalutamide, having water-solubility of $1 \cdot 10^{-3}$ mg/ml to $1 \cdot 10^{-2}$ mg/ml.

Thus, the subject of the present invention is a dosage form comprising enzalutamide in a dissolved form, a first solvent, a second solvent and optionally an oily component. In particular the subject of the present invention is a dosage form comprising

1 to 20 wt.% enzalutamide in a dissolved form,

10 to 80 wt.% of a first solvent, preferably 20 to 70 wt.%,

5 to 80 wt.% of a second solvent, preferably 10 to 70 wt.% and optionally an oily component.

It was found that due to the increased bioavailability the dosage form of the present invention can be prepared with a superior drug load and thus can be provided in a form being easy to swallow such that an excellent patient compliance can be achieved. Further, the dosage form of the present invention has an improved dissolution profile and can be very stable over a long period.

In a further aspect the present invention also relates to the use of a solvent having an HLB of 1 to 50 for producing an oil/water emulsion or a mycellic system of an API having water-solubility of $1 \cdot 10^{-3}$ mg/ml to $1 \cdot 10^{-2}$ mg/ml, when brought into contact with an aqueous solution, in particular with gastric fluid.

**Detailed Description of the Invention**

The chemical name of enzalutamide, also known as MDV-3100, is 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-$N$-methylbenzamide. Enzalutamide is reported to be an active agent having anti-tumor activity which belongs to the class of non-steroidal androgen receptor antagonists.
The chemical name of enzalutamide is \(4-(3-(4\text{-Cyano-3-}(\text{trifluoromethyl})\text{phenyl})-5,5\text{-dimethyl-4-oxo-2-thiooximidazolidin-1-yl})-2\text{-fluoro-}N\text{-methylbenzamide.}\)

Enzalutamide is characterized by the following formula (I)

\[
\text{H}_3\text{C}\text{N}\text{H} \quad \text{F} \\
\text{N} \quad \text{S} \\
\text{H}_3\text{C} \quad \text{N} \quad \text{N} \\
\text{H}_3\text{C} \quad \text{O} \quad \text{CF}_3
\]

formula (I)

In this regard it is noted that in the present invention the term "enzalutamide" comprises \(4-(3-(4\text{-Cyano-3-}(\text{trifluoromethyl})\text{phenyl})-5,5\text{-dimethyl-4-oxo-2-thiooximidazolidin-1-yl})-2\text{-fluoro-}N\text{-methylbenzamide according to formula (I). In addition the term "enzalutamide" comprises all the pharmaceutically acceptable salts, polymorphs, hydrates and/or solvates thereof. Enzalutamide can be obtained according to the procedures as outlined in WO 2006/124118.}

In a particularly preferred embodiment of the present invention enzalutamide is used in its free form, i.e. neither as a salt nor in hydrated/solvated form. Unless otherwise mentioned within the present application the amounts or weight-% of enzalutamide are based on the amount of enzalutamide in its free form.

In a particularly preferred embodiment the dosage form of the invention comprises enzalutamide as the sole pharmaceutically active agent.

In another preferred embodiment the dosage form of the invention can comprise enzalutamide in combination with further pharmaceutically active agent(s).
In the present invention enzalutamide can be present in a non-solid form, in particular enzalutamide can be present in dissolved form. Generally, the term "dissolved" refers to a partially or completely dissolved form. For example, enzalutamide can be present in dissolved form, wherein it is dissolved to an amount of at least 30 wt.%, preferably at least 50 wt.%, more preferably at least 70 wt.%, in particular at least 90 wt%. Preferably enzalutamide is present in a completely dissolved form.

The present enzalutamide can be referred to as dissolved enzalutamide, i.e. the molecules of the present component are preferably surrounded by a solvate shell. This solvate shell can be composed of several layers of solvent molecules wherein the molecules of the various layers of the solvate shell interact the less with the core molecule the further they are removed from said core molecule. Solvated molecules can preferably be regarded as a flexible entity which solvate shell is in interaction with solvent molecules. Due to the solvate shell the enzalutamide of the present invention can exhibit neither a periodic arrangement over a great range (= long-range order), such as usually known from crystalline substances, nor a certain regularity and similarity to the crystalline state with regard to the distance from and orientation towards their closest neighbours (= short-range order), as usually known from non-crystalline substances. Consequently, the present enzalutamide preferably does not show any tendency to agglomerate and to precipitate.

In a preferred embodiment of the present dosage form the first solvent can be an amphiphilic compound.

Generally, amphiphilic compounds, often also referred to as surfactants, are composed of a non-polar and a polar part. The non-polar part can be for example an alkyl chain or an alkyl phenyl group.
The polar part of the amphiphilic compound can be composed of various functional groups being suitable to classify the surfactant into the following four categories; i.e.

- anionic amphiphilic compounds having a negatively charged polar group such as a carboxylate, a sulfonate, sulfate or phosphate group,
- cationic amphiphilic compounds having a positively charged polar group such as a quaternary ammonium group,
- zwitterionic amphiphilic compounds having both a negatively charged polar group, such as a carboxylate, and a positively charged polar group, such as a quaternary ammonium group,
- non-ionic amphiphilic compounds having for example one or a plurality of hydroxy or ether group(s) or combinations thereof.

Anionic amphiphilic compounds (surfactants) can be for example sodium lauryl sulfate, sodium lauryl ether sulfate, dioctyl sodium sulfosuccinate, lauryl phosphate and sodium stearate.

Examples for cationic amphiphilic compounds are hexadecyl trimethyl ammoniumbromide and hexadecyl pyridinium chloride.

Zwitterionic amphiphilic compounds can be for example 3-((3-chloramidopropyl)diemthylammonio)- 1-propanesulfate, cocamidopropyl betaine and lecithin.

Non-ionic amphiphilic compounds can for example be fatty alcohols, polyoxyethylene glycol alkyl ethers, polyoxypropylene glycol alkyl ethers, glucoside alkyl ethers, polyoxyethylene glycol sorbitan alkyl ester, sorbitan esters block copolymers of polyethyleneglycol and polypropylene glycol, polyoxyethylene glycerol esters, polyoxyethylene sorbitol esters, polyoxyethylene sorbitan esters, polyoxyethylene esters, glycerol monoesters, glycerol diesters,
polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (marketed by BASF under the name Soluplus®) or mixtures thereof.

Polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer can be represented by the following formula

![Chemical structure](image)

Polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (Soluplus®)

Preferably 1, m and n are independently natural numbers from 10 to 400.

The average molecular weight of polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (Soluplus®) determined by gel permeation chromatography is preferably in the range of 90,000 to 140,000 g/mol.

It is preferred that the first solvent is a non-ionic amphiphilic compound, preferably a liquid non-ionic amphiphilic compound. The first solvent can be a solid or liquid (at 25 °C).
In preferred embodiment the first solvent has an HLB-value of 1 to 50, preferably 3 to 45, more preferably 8 to 40 and in particular 10 to 20.

The HLB-value (hydrophilic-lipophilic balance value) indicates the degree to which an amphiphilic compound is hydrophilic or lipophilic. It is determined by calculating values for the different regions of the molecule. The HLB as defined according to Griffin's method is calculated by the following equation:

\[
\text{HLB} = 20 - \left( \frac{M_h}{M} \right),
\]

wherein

- \( M_h \) is the molecular mass of the hydrophilic portion of the molecule, and
- \( M \) is the molecular mass of the whole molecule.

Thus, according to Griffin the HLB-value ranges from 0 to 20 and a small HLB value (for example from 0 to 3) indicates that the compound is a lipophilic/hydrophobic molecule and a high HLB-value represents a hydrophilic/lipophobic molecule.

Examples of preferred compounds are sorbitan esters (Span), especially from saturated or unsaturated fatty acids, polyethoxylated sorbitan esters (Tween), especially from saturated or unsaturated fatty acids, polyethoxylated glycerides (Labrasol), lauroyl macrogol-32 glycerides (Gelucire 44/14), stearoyl macrogol-32 glycerides (Gelucire 50/13), especially from saturated or unsaturated fatty acids, polyethoxylated and/or hydrogenated castor oils such as PEG-40 hydrogenated castor oil (Cremophor RH 40®), PEG-60 hydrogenated castor oil (Cremophor RH 60®), PEG-35 castor oil or polyoxyl 35 castor oil (Cremophor EL), Macrogol (25) cetostearyl ether (Cremophor A25), polyethoxylated ethers, especially from saturated or unsaturated fatty alcohols, polyethylene glycol such as PEG 200, poloxamer (Lutrol F 127), alpha tocopherol, polyoxyethylene lauryl ether (Brji 30, Brji 35), polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer (e.g. Soluplus®) and mixtures thereof.
PEG-35 castor oil or polyoxyl 35 castor oil (Cremophor EL) is a compound obtained by reacting castor oil with ethylene oxide in a molar ratio of about 1:35.

In an embodiment the first solvent has an HLB-value of 1.5 to 8, preferably from 1.8 to 8.0, more preferably from 3.0 to 7.5, especially from 3.2 to 7.2. Examples include for example sorbitan trioleate, sorbitan tristearate, sorbitan sesquioleate, sorbitan monooleate, sorbitan monostearate, sorbitan trioleate, sorbitan monopalmitate, sorbitan monolaurate, glyceryl monostearate, mono/diglycerides from coconut oil, primarily oleic acid polyglycolyzed glycerides from apricot kernel oil, primarily oleic acid polyglycolyzed glycerides from corn oil, glyceryl linoleate and alpha tocopherol.

In a particularly preferred embodiment the first solvent has an HLB-value of 9 to 20, preferably from 9.5 to 19, more preferably from 10 to 18, especially from 11 to 16.5. Examples include PEG (20) sorbitan monolaurate, PEG (4) sorbitan monolulate, PEG (20) sorbitan monolureate, PEG (20) sorbitan monostearate, PEG (4) sorbitan monostearate, PEG (20) sorbitan tristearate, PEG (80) sorbitan monololeate, polaxamer (Kollisolv™ P124), Macrogol (25)-cetostearyl ether, Macrogol (25)-cetostearyl ether, PEG-60 hydrogenated castor oil, polyoxyl 35 castor oil, polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (e.g. Soluplus®) and macrogol 20 glycerol monostearate. Especially preferred are PEG (20) sorbitan monolaurate, PEG (80) sorbitan monololeate, polaxamer (Kollisolv™ P124), PEG-35-castor oil or polyoxyl 35 castor oil (Cremophor EL) and macrogol 20 glycerol monostearate.

In case polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (e.g. Soluplus®) is used as first solvent it is preferred to use polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer in a mixture with at least one other first solvent.

In case of HLB determination of an ionic solvent (surfactant) the Griffith’s method can be inappropriate. In that case preferably "fictive" values are used. Such fictive
values are known in the art, see e.g. Fiedler, Lexikon der Hilfsstoffe, 5th edition 2002, page 121. Substances and the corresponding HLB-values are for example
- N-cetyl-N-ethyl morpholinium ethosulfate: HLB of 30,
- triethanolamine lauryl sulfate: HLB of 34,
- sodium lauryl sulfate: HLB of 40,
- sodium 2-ethylhexyl-sulfate: HLB of 42,
- sodium octyl sulfate: HLB of 42, and
- soy lecithin: HLB of 80.

In a preferred embodiment the dosage form of the present invention comprises a second solvent, wherein preferably the second solvent is different from the first solvent.

Besides the first solvent the dosage form of the present invention preferably comprises a second solvent.

In a preferred embodiment the second solvent has a water solubility at 25°C of more than 30 wt.%, preferably more than 50 wt.%, more preferably more than 70 wt.%, in particular more than 90 wt.%. The upper limit of the water solubility can be 90 wt.% or preferably 100 wt.%. The water solubility can be determined via visual inspection, i.e. the portion of second solvent to water is determined until precipitation or until a suspension or until a phase separation between water and second solvent appears.

In a preferred embodiment of the invention the second solvent has a logK_{ow}-value of -3 to 0.7, preferably of -2.5 to 0.5, more preferably of -2 to 0.3, in particular of -1.8 to 0.

The K_{ow}-value (also known as P-value) is a distribution coefficient (partition coefficient) indicating the ratio of concentrations of a compound in the two phases of an octanol/water (hydrophobic/hydrophilic) mixture. The K_{ow}-value is determined according to the following formula
\[ K_{ow} = P = \frac{c_{o}^{s_i}}{c_{w}^{s_i}}, \]

wherein

- \( c_{o}^{s_i} \) is the concentration of the species \( i \) of a chemical compound in the octanol phase and
- \( c_{w}^{s_i} \) is the concentration of the species \( i \) of a chemical compound in the water phase.

The \( K_{ow} \)-value (P-value) is generally used in form of the decade logarithm as \( \log K_{ow} \).

\[ \log K_{ow} = \log P = \log \frac{c_{o}^{s_i}}{c_{w}^{s_i}} \]

Examples for the second solvent are polyethylene glycols such as tetraethylene glycol to decaethylene glycol, glycerol, copolymers of polyoxypropylene and polyoxyethylene (Polaxamer 124), alkyl diols such as butanediol, triols such as 1,2,6 hexantriols, propylene glycols such as 1, 2 propylene glycol, DMSO (dimethyl sulfoxide), dimethyl isorbide, tetraglycol, solketal and diethylene glycol monoethyl ether (Transcutol HP) and mixtures thereof. More preferably propylene glycols such as 1,2 propylene glycol, dimethyl sulfoxide (DMSO), dimethyl isorbide, tetraglycol, solketal and diethylene glycol monoethyl ether (Transcutol HP) and mixtures thereof are used as second solvent.

Regarding the first and the second solvent it is noted that in a preferred embodiment of the present invention caprylocaproyl polyoxyglycerides do not constitute the first and the second solvent. In another embodiment caprylocaproyl polyoxyglycerides do neither constitute the first nor the second solvent. In a preferred embodiment the present invention does not encompass a liquid-filled soft gelatin capsules for oral administration, wherein the capsule contains 40 mg of
enzalutamide as a solution in caprylocaproyl polyoxylglycerides, wherein further the contains butylated hydroxyanisole and butylated hydroxytoluene, and wherein optionally the capsule shell contains gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide and black iron oxide.

In a preferred embodiment the dosage form of the present invention additionally comprises an oil (hereinafter also referred to as oily component).

In a preferred embodiment the oily component has a water solubility at 25°C of 0 to 10 wt.%, preferably 0.0001 to 5 wt.%, more preferably 0.001 to 2 wt.%, in particular 0.01 to 1 wt.%. The water solubility can be determined via visual inspection, i.e. the portion of second solvent to water is determined until precipitation or until a suspension or until a phase separation between water and second solvent appears.

In a preferred embodiment the oily component is a glycol-diester or a glycerol-triester (triglyceride), preferably a triglyceride.

The oily component can preferably be a vegetable oil. At room temperature (25°C) vegetable oils preferably show flowability, i.e. they are in a liquid state. In a preferred embodiment the oily component is a triclyceride, preferably a triglyceride with ester with fatty acid(s). Fatty acids suitable to form a triglyceride are saturated fatty acids such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid or unsaturated fatty acids such as oleic acid, linoleic acid, alpha linolenic acid or gamma linolenic acid, or mixtures thereof.

Examples of the oily component are glycerol trioleate, olive oil, castor oil, sunflower oil, soybean oil, canola oil, palm oil, linseed oil, peanut oil, $C_9/C_{10}$ triglycerides from coconut oil (Myglyol 812) and mixtures thereof.
More preferred are glycerol trioleate, olive oil, castor oil, sunflower oil, soybean oil, Cg/Cio triglycerides from coconut oil (Myglyol 812) and mixtures thereof, in particular (Myglyol 812).

In a preferred embodiment of the present dosage form the weight ratio of the first solvent to the second solvent can be from 5:1 to 1:2, preferably from 4:1 to 1:2, more preferably from 3:1 to 1:1.5 and particularly from 2:1 to 1:1.

In alternative preferred embodiment of the present dosage form the weight ratio of the first solvent to the second solvent can be from 2:1 to 1:5, preferably from 1.7:1 to 1:4.5, more preferably from 1.5:1 to 1:4 and particularly from 1:2:1 to 1:3.5.

It turned out that with the use of the first and second solvents, preferably in the above weight ratio, the enzalutamide can be favourably transferred in the dissolved form and stabilized in acid conditions occurring in the stomach. Consequently, a superior in-vitro and in-vivo dissolution profile can be achieved with the present dosage form compared to the one known from the prior.

In a preferred embodiment of the present invention the dosage form contains 1 to 20 wt.%, e.g. 2.5 to 10 wt.%, preferably 3.0 to 9 wt.%, more preferably 3.2 to 8.5 wt.%, in particular 3.5 to 8.0 wt.% enzalutamide,

10 to 80 wt.%, e.g. 30 to 70 wt.%, preferably 33 to 66 wt.%, more preferably 36 to 62 wt.%, in particular 40 to 60 wt.% first solvent,

5 to 80 wt.%, e.g. 14 to 60 wt.%, preferably 17 to 63 wt.%, more preferably 20 60 wt.%, in particular 25 to 55 wt.% second solvent, and optionally

0 to 20 wt.%, e.g. 5 to 15 wt.%, preferably 6 to 4 wt.%, more preferably 7 to 13 wt.%, in particular 8 to 12 wt.% oily component.

Preferably, in case a capsule is used (as described hereinafter), the above amounts refer to the amounts of the filling matrix only and not to the amounts of the filling matrix and the shell.
It is preferred that in the present dosage form the amount of enzalutamide is from 10 to 250 mg, preferably from 20 to 160 mg, more preferably from 30 to 120 mg, in particular from 35 to 85 mg.

In a particularly preferred embodiment in the present dosage form the amount of enzalutamide is 40 mg.

In an alternative particularly preferred embodiment in the present dosage form the amount of enzalutamide is 80 mg.

In a preferred embodiment for preparing a dosage form containing 80 mg enzalutamide a first solvent containing polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer (Soluplus®) and a second solvent containing diethylene glycol monoethyl ether (Transcutol HP) can be used.

In an alternative particularly preferred embodiment in the present dosage form the amount of enzalutamide is 160 mg.

The dosage form of the present invention (e.g. capsules) can provide as immediate release ("IR") of enzalutamide. This means that the release profile of the dosage forms of the invention according to United States Pharmacopeia (USP), Apparatus Typ II (paddle), 900 mL, 0.1 N HCl; pH 1.2; 37°C 50 rpm usually indicates a content release of at least 70 %, preferably at least 80 %, especially at least 85 % after 10 minutes. As it can be seen the condition for determination the dissolution substantially corresponds to simulated gastric fluid. Furthermore, the dosage form of the present invention provides enzalutamide in stabilized form under acidic conditions. That means, contrary to the prior art the dosage form of the present invention remains in dissolved form, e.g. after 15 and after 20 minutes. Hence, the release profile of the dosage forms of the invention according to United States Pharmacopeia (USP), Apparatus Type II (paddle), 900 mL, 0.1 N HCl; pH 1.2; 37°C 50 rpm usually indicates a content release of at least 70 %, preferably at least 80 %, especially at least 85 % after 15 minutes and after 20 minutes.
A high dissolution over a significant period of time of the present dosage form results in a superior bioavailability of the drug within the human organism.

In a preferred embodiment the present dosage form can preferably contain one or more antioxidants. Antioxidants are compounds for the protection of the used components from oxidation, preferably the first solvent and the oily component, especially the first solvent. Examples for suitable antioxidants comprise ascorbyl palmitate, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate and mixtures thereof. Antioxidants are used in an amount up to 2.0 wt.%, preferably 0.1 to 1.8 wt.%, in particular 0.2 to 1.6 wt.%. 

In an embodiment of the present invention the combination of butylated hydroxytoluene and butylated hydroxyanisole is not used as antioxidants, provided that caprylocaproyl polyoxyglycerides are used as first and the second solvent.

In a preferred embodiment the present dosage form can preferably comprise one or more pharmaceutical excipient(s). The pharmaceutical excipients and their amounts are excipients with the corresponding amounts with which the person skilled in the art is familiar, such as those which are described in the European Pharmacopoeia (Ph.Eur.) and/or in the US Pharmacopoeia (USP).

The dosage form of the present invention can be preferably an oral dosage form, more preferably a solid oral dosage form.

In a possible embodiment the dosage can be a tablet.

In an alternative preferred embodiment the dosage form is a capsule, preferably a soft capsule, in particular a soft gelatine capsule. Alternatively preferred the capsule is a hard capsule, e.g. a hard gelatine capsule.

In a preferred embodiment the soft capsule comprises a shell, and
a fill matrix.

Preferably, the fill matrix contains or consists of the above-described dissolved enzalutamide (i.e. enzalutamide in dissolved form and optionally first solvent, second solvent and oily compound). The shell preferably has a thickness of 0.2 to 1.8 mm.

In a preferred embodiment the shell comprises gelatin, optionally a plasticizer and optionally water and optionally colorants and/or flavours. For producing such a shell, a wet gel formulation is processed as described below.

Preferably, alkali processed (type B) gelatin is used. Preferably, gelatin is used in an amount of 40 wt.% of the wet gel formulation.

Preferably glycerol, sorbitol or propylene glycol are used as plasticizer. Plasticizers usually are used in an amount of 20 - 30 wt.% of the wet gel formulation.

In an alternative embodiment the shell preferably does not contain any plasticizers. In particular, the shell preferably does not contain any plasticizers selected from citric acid esters, phthalates, triacetin and mixtures thereof.

Water usually is used in an amount of 30-40 wt.% of the wet gel formulation.

Usually, the wet gel formulation is prepared by dissolving the gelatine in water (e.g. at 70 to 85°C), followed by the addition of plasticizer and optionally colorant/flavours. The wet gel formulation is then supplied to an encapsulation machine, preferably through transfer pipes by a casting method that forms two separate gelatine ribbons. Each gel ribbon may be suitable for providing half of the soft capsule.
The fill matrix containing the dissolved enzalutamide (i.e. enzalutamide in dissolved form and optionally first solvent, second solvent and oily compound) can be manufactured separately.

Preferably, the gel ribbons and the fill matrix are combined to form the softgel capsule by a rotary die encapsulation process. Usually, metered volumes of the liquid fill matrix are injected, e.g. from a wedge device, into the space between the gelatine ribbons. The two softgel capsule halves can be sealed together, e.g. by the application of heat and pressure. The sealed body of the capsule can preferably not be opened without visible damage and it is preferably tamper-evident. Further, the capsule can preferably be highly impermeable.

For example, the capsule liquid filling and sealing system CFS 1200 by CAPSUGEL® can be used.

After the encapsulation process water can be removed. Preferably, the shell has a residual water content of about 5 to 35 wt.%, more preferably of about 7 to 15 wt.%.

It is alternatively preferred that the solid oral dosage form is a hard capsule. Hard capsules known also as two-pieces capsules can be formed by two precast cylinders each being hemispherically sealed at one end, respectively.

The hard gelatine capsules can preferably have a volume from 0.02 to 1.37 ml, more preferably from 0.1 to 0.91 ml.

Hard capsules can preferably be produced using gelatine or other pharmaceutically acceptable materials, preferably polymers such as hydroxypropyl methylcellulose. The capsules may be dyed by adding dyes during the production process.

The preparation of hard capsules can preferably be carried out according to the Colton process in which pins are dipped into an aqueous gelatine or polymer
solution such that the pins are covered with a thin film of gelatine or polymer wherein the film is further solidified and dried.

Hard gelatine capsules preferably comprise gelatine, water and optionally dye. It is preferred that hard gelatine capsules do not comprise further components, in particular no plasticizers.

The hard capsules can be preferably filled with liquid, semi-solid or solid pharmaceutical compositions.

A further subject of the present invention is the use of a solvent, preferably having an HLB of 1 to 50, more preferably 3 to 45, even more preferably 8 to 40 and in particular 10 to 20 for producing a water/oil emulsion of an API having a water-solubility of $1 \cdot 10^{-3}$ to $1 \cdot 10^{-2}$ mg/ml. It is further preferred that the solvent is a mixture of a solvent having an HLB of 1 to 20, more preferably of 9 to 20, even more preferably of 9.5 to 19, in particular of 10 to 18, especially of 11 to 16.5 and a solvent having a log$K_{ow}$-value of -3.0 to 0.7, preferably of -2.5 to 0.5, more preferably of -2 to 0.3, in particular of -1.8 to 0.

It turned out that the use of such a specific mixture of solvents enables the formation of a water/oil emulsion of an API having a water-solubility of $1 \cdot 10^{-3}$ to $1 \cdot 10^{-2}$ mg/ml and that the dissolution of the API is significantly enhanced by said procedure. Water-solubility is determined in the context of this invention using the column elution method in accordance with EU Directive DIR 67-548 EEC, Annex V, Chap. A6, measured at 25 °C.

In a further preferred embodiment the API can be an anti-tumoral compound. A tumor can be regarded as the increase of the volume of the tissue. Thus, an anti-tumoral compound is considered to be a drug showing activity against a tumor, preferably against a malignancy, in particular against cancer. Examples of cancers to be treated with an anti-tumoral compound comprise intestinal cancer, laryngeal
cancer, breast cancer, prostate cancer and testicular cancer. Enzalutamide is a preferred embodiment of said anti-tumoral compound.

A further aspect of the present invention is a dosage form comprising enzalutamide, wherein the enzalutamide is dissolved in a particular solvent having a logK<sub>ow</sub>-value of -3.0 to 0.7, preferably of -2.5 to 0.5, more preferably of -2 to 0.3, in particular of -1.8 to 0. A preferred example of said particular solvent is diethylene glycol monoethyl ether (Transcutol HP). In case a particular solvent, e.g. diethylene glycol monoethyl ether (Transcutol HP) is used, said solvent may function as first and as second solvent. In other words, dissolving enzalutamide in said particular solvent may achieve the above-mentioned benefits of the present invention. For the dosage form comprising enzalutamide, wherein the enzalutamide is dissolved in said particular solvent having a logK<sub>ow</sub>-value of -3.0 to 0.7, generally the same explanations (e.g. regarding preferred embodiments) apply as in the above-mentioned dosage form of the present invention.

Preferably the dosage form of the second aspect of the present invention comprises 1-20 wt.%, preferably 2.5 to 10 wt.%, more preferably 3.0 to 9 wt.% enzalutamide, 50-99 wt.%, preferably 60 to 97.5 wt.%, more preferably 80 to 97 wt.% diethylene glycol monoethylether, and optionally 0-49 wt.%, preferably 1 to 42.5 wt.%, more preferably 5 to 30 wt.% further excipients.

Preferably, in case a capsule is used, the above amounts refer to the filling matrix only and not to the amounts of the filling matrix and the shell.

Further the present invention relates to a process for stabilizing enzalutamide in micelle form, preferably in micelle form under conditions occurring in the human stomach, comprising the steps of

a) dissolving enzalutamide in a first solvent, optionally a second solvent and optionally an oil,
b) bringing the mixture of step a) in contact with an aqueous solution or suspension, wherein the weight ratio of the enzalutamide solution of step a) to the aqueous solution or suspension in step b) is from 1:50 to 1:1000.

Step b) can be carried out by administering the dissolved enzalutamide to a human.

It turned out that due to the stabilization in micelle form the dissolution of enzalutamide can be significantly enhanced and thus enzalutamide is provided in a form with superior bioavailability.

Another subject of the present invention is a process for increasing the bioavailability of enzalutamide, wherein enzalutamide is administered perorally in dissolved form, said dissolved form comprising a first solvent, a second solvent and optionally an oily component.

The invention will now be explained with reference to the following examples.

Examples

Example 1

PEG (80) sorbitan monooleate (Tween 80), diethylene glycol monoethylether (Transcutol HP) and caprylic/capric triglyceride (Myglyol 812) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising
Enzalutamide 40 mg 3.8 wt.%
PEG (80) sorbitan monooleate 600 mg 57.7 wt.%
Diethylene glycol monoethylether 300 mg 28.8 wt.%
Caprylic/capric triglyceride 100 mg 9.6 wt.%

1040 mg 100 %

Example 2

PEG (20) sorbitan monooleate (Tween 20), diethylene glycol monoethylether (Transcutol HP) and caprylic/capric triglyceride (Myglyol 812) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

Enzalutamide 40 mg 3.8 wt.%
PEG (20) sorbitan monooleate 400 mg 38.5 wt.%
Diethylene glycol monoethylether 500 mg 48.1 wt.%
Caprylic/capric triglyceride 100 mg 9.6 wt.%

1040 mg 100 %

Example 3

PEG-35 castor oil (Cremophor EL) and dimethyl sulfoxide (DMSO) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

Enzalutamide 40 mg 3.8 wt.%
PEG-35 castor oil 600 mg 57.7 wt.%
dimethyl sulfoxide 400 mg 38.5 wt.%

1040 mg 100 %
Example 4

PEG-35 castor oil (Cremophor EL) and PEG400 were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

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Example 5

PEG (80) sorbitan monooleate (Tween 80), diethylene glycol monoethylether (Transcutol HP) and polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer (Soluplus®) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

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<td>polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer</td>
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<td>5 wt.%</td>
</tr>
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<td>Diethylene glycol monoethylether</td>
<td>730 mg</td>
<td>73 wt.%</td>
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<td>1000 mg</td>
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</table>

Example 6

PEG (80) sorbitan monooleate (Tween 80), diethylene glycol monoethylether (Transcutol HP) and polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol
graft copolymer (Soluplus®) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

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<tr>
<td>PEG (80) sorbitan monooleate</td>
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<td>polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer</td>
<td>40 mg</td>
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**Example 7**

PEG (80) sorbitan monooleate (Tween 80), diethylene glycol monoethylether (Transcutol HP) and polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer (Soluplus®) were mixed together and subsequently enzalutamide was added to the mixture. The final mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

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<td>polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer (Soluplus®)</td>
<td>30 mg</td>
<td>3.0 wt.%</td>
</tr>
<tr>
<td>diethylene glycol monoethylether</td>
<td>730 mg</td>
<td>74.5 wt.%</td>
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<td>980 mg</td>
<td>100 %</td>
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**Reference Example 1**

Caprylocaproyl polyoxyl-8 glycerides (Labrasol®) and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

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<tbody>
<tr>
<td>Enzalutamide</td>
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<td>3.8 wt.%</td>
</tr>
<tr>
<td>Caprylocaproyl polyoxyl-8 glycerides</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
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</table>

**Reference Example 2**

Dimethyl sulfoxide (DMSO) and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

<p>| | | |</p>
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
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<tr>
<td>dimethyl sulfoxide</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
</tbody>
</table>

**Reference Example 3**

PEG-35 castor oil (Cremophor EL) and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

<p>| | | |</p>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>40 mg</td>
<td>3.8 wt.%</td>
</tr>
<tr>
<td>PEG-35 castor oil</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
</tbody>
</table>
Reference Example 4

PEG400 and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

<table>
<thead>
<tr>
<th>Enzalutamide</th>
<th>40 mg</th>
<th>3.8 wt.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG400</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Reference Example 5

PEG (80) sorbitan monooleate and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

<table>
<thead>
<tr>
<th>Enzalutamide</th>
<th>40 mg</th>
<th>3.8 wt.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG (80) sorbitan monooleate</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Reference Example 6

Diethylene glycol monoethylether (Transcutol) and enzalutamide were mixed together. The mix was well stirred for 15 minutes at 50°C to disperse/solubilize the active pharmaceutical ingredient to obtain a composition comprising

<table>
<thead>
<tr>
<th>Enzalutamide</th>
<th>40 mg</th>
<th>3.8 wt.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylene glycol monoethylether</td>
<td>1000 mg</td>
<td>96.2 wt.%</td>
</tr>
<tr>
<td></td>
<td>1040 mg</td>
<td>100 %</td>
</tr>
</tbody>
</table>
Reference Example 7

Commercially available Xtandi® was subjected to dissolution. The capsule contains 40 mg of enzalutamide and the following excipients: caprylocaproyl poloxylglycerides ([Laprasol] as solubilizer), butylated hydroxyanisole and butylated hydroxytoluene (antioxidants).

Results

The formulations of Example 1 through 7 and Reference Examples 1 through 7 have been subjected to dissolution testings. Conditions: USP Type II (paddle), 900 ml, 0.1 N HCl, pH 1.2, 37 °C, 50 rpm.

In Figure 1 the dissolution profiles of Example 1, Reference Example 1, Reference Example 5 and Reference Example 6 are shown. It can be seen that the combination of Transcutol (first solvent) and Tween 80 (second solvent) is unexpectedly superior to the formulations with each of the components alone.

In Figure 2 the dissolution profiles of Example 1 and Example 2 are shown. It can be seen that the Tween 80 and Tween 20 are equally suitable.

In Figure 3 the dissolution profiles of Example 3, Reference Example 1, Reference Example 2 and Reference Example 3 are shown. It can be seen that the combination of Cremophor EL (first solvent) and DMSO (second solvent) is unexpectedly superior to the formulations with each of the components alone.

In Figure 4 the dissolution profiles of Example 4, Reference Example 1, Reference Example 3 and Reference Example 4 are shown. It can be seen that the combination of Cremophor EL (first solvent) and PEG400 (second solvent) is unexpectedly superior to the formulations with each of the components alone.

In Figure 5 the dissolution profiles of Example 5, Example 6 and Example 7 as well as Reference Examples 1 and 7 are shown. It can be seen that the twice as
much active ingredient enzalutamide (80 mg) can be formulated with the combination of Tween 80 and Soluplus (first solvents) and Transcutol (second solvent). These formulations are superior to the Reference Example 1 and the commercially available product Xtandi with 40 mg enzalutamide and labrasol (first solvent).
Claims

1. Dosage form comprising
   1 to 20 wt.% enzalutamide in a dissolved form,
   10 to 80 wt.% of a first solvent,
   5 to 80 wt.% of a second solvent, and
   optionally an oily component.

2. Dosage form according to claim 1, wherein the first solvent is an
   amphiphilic compound.

3. Dosage form according to claim 1 or 2, wherein the first solvent has an
   HLB-value of 1 to 50.

4. Dosage form according to any of the preceding claims, wherein the second
   solvent has a logK_{ow}-value of -3 to 0.7.

5. Dosage form according to any of the preceding claims, wherein the second
   solvent is selected from polyethylene glycols, glycerol, copolymers of
   polyoxypolyethylene and polyoxyethylene, alkyl diols, alkyl triols, propylene
   glycols, DMSO, dimethyl isorbid, tetruglycol, solketal and diethylene
   glycol monoethyl ether and mixtures thereof.

6. Dosage form according to any of the preceding claims, wherein the oily
   component is a triglyceride.

7. Dosage form according to any of the preceding claims, wherein the weight
   ratio of first solvent to second solvent is 5:1 to 1:2.

8. Dosage form according to any of the preceding claims, wherein the dosage
   form is a solid dosage form, and wherein the dosage form preferably
   comprises
   3 to 10 wt.% enzalutamide,
10 to 70 wt.% first solvent,
14 to 80 wt.% second solvent, and optionally
5 to 15 wt.% oily component.

9. Dosage form according to any of the preceding claims, wherein the dosage form contains 40 to 160 mg enzalutamide.

10. Dosage form according to any of the preceding claims, wherein the dosage form contains 40, 80 or 160 mg enzalutamide.

11. Dosage form according to any of the preceding claims, wherein the dosage form contains 80 mg enzalutamide, a first solvent containing polyvinyl caprolactam-polyvinylacetate-polyethyleneglycol graft copolymer and a second solvent containing diethylene glycol monoethyl ether.

12. Dosage form according to any of the preceding claims showing a dissolution of at least 70% after 10, 15 and 20 minutes, determined according to USP type II, paddle, 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm.

13. Dosage form comprising enzalutamide, wherein the enzalutamide is dissolved in diethylene glycol monoethyl ether.

14. Dosage form according to any one of the preceding claims, wherein the dosage form is a capsule, comprising

a shell and

a fill matrix, wherein the fill matrix comprises the dissolved enzalutamide.

15. Use of a solvent having an HLB of 1 to 50 for producing an oil/water/oil emulsion or a mycellic system of an active pharmaceutical ingredient, preferably an anti-tumoral compound, having a water-solubility of $1 \times 10^{-3}$ mg/ml to $1 \times 10^{-2}$ mg/ml, when brought into contact with an aqueous solution.

16. Use according to claim 15, wherein the solvent is a mixture of a solvent with an HLB of 1 to 50 and a solvent having a logK_{ow}-value of -3 to 0.7.
17. Use of a solvent mixture comprising polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer and diethylene glycol monoethyl ether for dissolving 80 mg of enzalutamide in a capsule.

18. Process for stabilizing enzalutamide in micelle form, comprising the steps of:
   a) dissolving enzalutamide in a first solvent, optionally a second solvent and optionally an oily component;
   b) bringing the mixture of step a) in contact with an aqueous solution or suspension,
   wherein the weight ratio of the enzalutamide solution of step a) to the aqueous solution or suspension in step b) is from 1:50 to 1:1000.

19. Process for increasing the bioavailability of enzalutamide, wherein enzalutamide is administered perorally in dissolved form, said dissolved form comprising:
   a first solvent,
   a second solvent, and
   optionally an oily component.
Figure 1/5

Dissolution of Enzalutamide Formulations
Conditions: 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm paddle (USP app. II)
Dissolution of Enzalutamide Formulations

Conditions: 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm paddle (USP app. II)

Figure 2/5
Dissolution of Enzalutamide Formulations

Conditions: 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm paddle (USP app. II)
Dissolution of Enzalutamide Formulations

Conditions: 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm paddle (USP app. II)
Dissolution of Enzalutamide Formulations

Conditions: 900 mL 0.1N HCl; pH 1.2; 37°C; 50 rpm paddle (USP app. II)
A CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61K9/48 A61K31/5025
ADD.

According to International Patent Classification (IPC) and 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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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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
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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
  - "Z" document member of the same patent family

Date of the actual completion of the international search
20 October 2014

Date of mailing of the international search report
29/10/2014

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer
Toulacis, C

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>WO 03/101378 A2 (STRIDES ARCOLAB LTD [IN]) 11 December 2003 (2003-12-11) paragraphs [0027] - [0037]; claims 1-31; table 1</td>
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