PATENT ATTORNEYS EXAMINATION – DECEMBER 2013

Dear Candidates,

Below is an invention disclosure received from the inventor.

Please draft a patent application based on the attached text taking into consideration the prior art disclosed in WO 2007/041053 and WO 2007/078726.

The draft is to be sent to the inventor and you may intercalate questions with questions regarding the invention and/or request for additional data, if you find necessary.

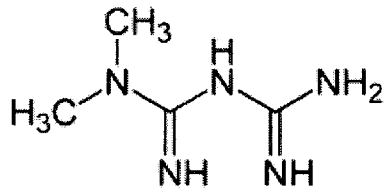
As a patent attorney, you are requested to:

1. Edit the text below such as to include the following sections: Title of the Invention, Background of the Invention, Summary of the Invention, and Detailed Description of the Invention comprising the Examples (25 points)
2. Draft a set of 10-15 claims that you believe would be patentable in Israel, Europe and in the US (60 points)
3. Explain your strategy to the inventor regarding the drafting of the claims (15 points)

Good Luck!

INVENTION DISCLOSURE

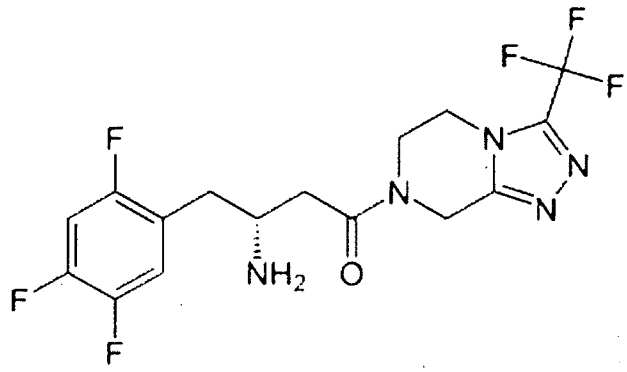
Metformin is a drug from the biguanides group, which is used in non-insulin-dependent diabetes (type 2 diabetes mellitus) and, in particular, for excess weight and obesity. Metformin is one of the antidiabetics longest in use. Metformin is the 1,1-dimethylbiguanide with the following structural formula:



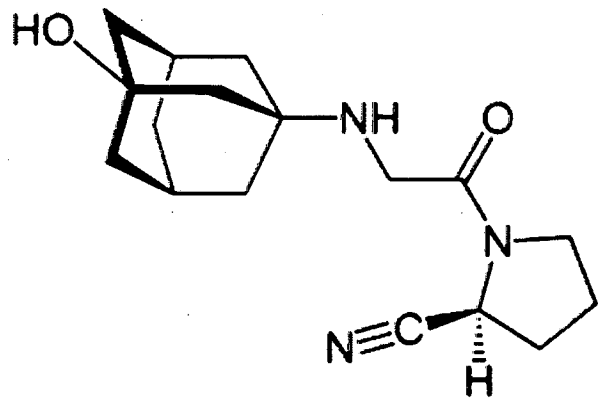
Metformin is available commercially in strengths of 500 mg, 850 mg and 1000 mg, to allow adjustment to an individual blood sugar level. The tablets are administered orally. Metformin is used first as monotherapy. If this does not produce a sufficient lowering of blood sugar, it is known to combine the active substance with other oral antidiabetics.

Oral antidiabetic drugs that may be combined with metformin include the dipeptidyl peptidase-4 inhibitors, also known as DPP-4 inhibitors or gliptins. Examples of known DPP-4 inhibitors approved for use as oral antidiabetics include sitagliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, teneligliptin and alogliptin.

Sitagliptin is (*R*)-3-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazole[4,3-*a*]pyrazin-7-yl]-4-(2,3,5-trifluorophenyl)butan-1-one, which has the following structural formula:



Vildagliptin is (2*S*)-{((3-hydroxyadamantan-1-yl)amino)acetyl}pyrrolidine-2-carbonitrile with the following structural formula:



Combination preparations of sitagliptin and metformin are known and obtainable under the trade names Janumet® and Velmecia®, and a combination preparation of vildagliptin and metformin is obtainable under the trade name Eucreas®.

Combination preparations of metformin and vildagliptin are described in WO 2007/041053. The tablets disclosed can contain, in addition to the active substances, usual excipients, for example fillers, binders, disintegrants, lubricants and colorants. Examples of lubricants that are mentioned are colloidal silica, magnesium trisilicate, starch, talc, calcium phosphate, magnesium stearate, aluminium stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, cellulose and microcrystalline cellulose. It is said to be possible for the lubricant to be present in an amount of up to 6 wt.%. In the examples, the tablets are produced by methods of wet granulation.

WO 2007/078726 discloses combination preparations that contain 3 to 20 wt.% of dipeptidyl-peptidase-4 inhibitor, 25 to 94 wt.% of metformin hydrochloride, 0.1 to 10 wt.% of lubricant and 0 to 35 wt.% of binder. The lubricants mentioned are magnesium stearates, calcium stearates, stearic acid, sodium stearyl fumarate and hydrogenated castor oil. The tablets, which are produced in the examples by methods of wet granulation, preferably contain only up to 2 wt.% of lubricant.

The combination preparations described in the prior art have the drawback that the tablets can only be produced by wet granulation, as the active substance metformin is a very poorly compressible active substance. In wet granulation there is, however, the risk that the active substance will either be decomposed through interactions with the solvent used, and undesirable degradation products will be formed.

The inventor says that there is still a need for pharmaceutical compositions that contain the active substance metformin in combination with one DPP-4 inhibitor such as sitagliptin or vildagliptin, and that can be produced by a simple method, preferably by direct compression. At the same time, addition of further excipients should not cause the tablets to become so large that they are difficult to swallow. Finally, the excipients must be selected so as to ensure rapid release of the active substances from the tablet.

The inventor believes that he found how to solve the problems of the prior art by using a high lubricant concentration such as more than 10 wt.% of lubricant for processing the active substances into the pharmaceutical composition. The use of high lubricant concentrations in the pharmaceutical composition is all the more surprising, as it is known that the advantage of their lubricating action is often opposed by the disadvantage of hydrophobisation of the product and therefore a lengthening of the disintegration time or of the dissolution rate of the tablet, so that lubricants should be used in the lowest possible concentration (Schmidt Christin, Wirk- und Hilfsstoffe (Active substances and excipients), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1999). Contrary to these known disadvantages of lubricants, the inventor found that if the lubricant is or comprises

polyethylene glycol, it can be used in high concentration of more than 10 wt.% and nevertheless tablets with a high dissolution rate are obtained, which can moreover be produced by direct compression.

The active substance metformin can be used in the invention preferably as pharmaceutically compatible salt and in particular as hydrochloride salt.

The active substance sitagliptin is preferably used in the form of one of its pharmaceutically compatible salts. Pharmaceutically compatible salts of sitagliptin are described for example in WO 2003/004498. Particularly preferably, sitagliptin is used as its phosphate salt, in particular as phosphate monohydrate. The corresponding salt and its production are disclosed in WO 2005/003135. Alternatively, the active substance sitagliptin can be used as hydrochloride, sulphate, mesylate, besylate, tosylate or mono-, di- or tricarboxylic acid salt. Suitable carboxylic acids have the structure R^1-COOH, in which R^1 is hydrogen, carboxyl, C_{1-4}-alkyl or C_{2-4}-alkenyl and the alkyl or alkenyl group can be substituted with 1-2 carboxyl, 1-3 hydroxyl, 1-3 amino, 1-3 phenyl and/or 1-3 C_{1-5}-alkyl residues. Preferred carboxylic acids are fumaric acid, malonic acid, malic acid, succinic acid, lactic acid, glycolic acid, maleic acid, citric acid, aspartic acid and mandelic acid.

The active substance vildagliptin can be used in the form of its free base or, if desired, in the form of a pharmaceutically compatible salt thereof. Pharmaceutically compatible salts of vildagliptin are disclosed in WO 2000/034241.

The amounts of the active substances in the combination composition can be freely selected by a person skilled in the art depending on the desired dosage. Preferably the pharmaceutical composition contains 25 to less than 87 wt.% of metformin hydrochloride, 3 to 20 wt.% of sitagliptin or vildagliptin or a pharmaceutically compatible salt of one of these active substances, calculated on the basis of the free base of the active substance, and more than 10 to 30 wt.% of lubricant, in each case relative to the total weight of the composition. It is to be noted that in the present text, the figures for percentage by weight, if they relate to the total weight of the composition, are relative to the weight of the

composition, but without any tablet coatings in the form of varnish layers, etc. that may be present.

The pharmaceutical composition may be a composition with a fixed dose of the active substances, wherein both active substances are contained together in a unit dose, in particular a tablet.

The amounts of the active substances are preferably selected so that a unit dose of the pharmaceutical composition contains 50 mg or 100 mg of sitagliptin or vildagliptin, in each case calculated on the basis of the free base of the active substance, and 500 mg, 850 mg or 1000 mg of metformin hydrochloride. A particularly preferred tablet contains 50 mg of sitagliptin or vildagliptin, calculated on the basis of the free base of the active substance, and 1000 mg of metformin hydrochloride.

The pharmaceutical composition should contain, in addition to the active substances, necessarily a high concentration, particularly more than 10 wt.%, of lubricant relative to the total weight of the composition. The lubricant is either polyethylene glycol or a mixture of polyethylene glycol with one or a plurality of other lubricants. The pharmaceutical composition preferably contains 12 to 28 wt.%, preferably more than 15 to 28 wt.%, for example 15.1 to 24 wt.%, particularly preferably 16 to 24 wt.%, for example about 19 wt.% of lubricant, in each case relative to the total weight of the composition.

The polyethylene glycol used preferably has a molecular weight of at least 1000 g/mol. The molecular weight of the polyethylene glycol is preferably in the range from 1000 to 20000 g/mol, particularly preferably in the range from 6000 to 10000 g/mol. A preferred polyethylene glycol is PEG 8000.

If the lubricant is a mixture of polyethylene glycol and one or more other lubricants, the polyethylene glycol can be mixed with conventional known lubricants, for example magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated castor oil, talc, fumaric acid, starches, for example pea, wheat, maize, potato, rye, rice, algal

or tapioca starch, sodium lauryl sulphate, colloidal silica, magnesium trisilicate, calcium phosphate, aluminium stearate, magnesium carbonate, magnesium oxide, cellulose and microcrystalline cellulose. Preferably the polyethylene glycol is mixed with one or a plurality of other lubricants, selected from the group consisting of talc, starch and sodium lauryl sulphate.

The mixture ratio of the lubricants used can be freely selected by a person skilled in the art depending on the desired properties of the pharmaceutical composition. The lubricant mixture should preferably contain at least 10 wt.%, preferably at least 50 wt.% and particularly preferably at least 85 wt.% of polyethylene glycol relative to the total weight of the lubricants.

In order to influence the release properties of the pharmaceutical composition, sodium lauryl sulphate can be used as lubricant addition. In this case the amount of sodium lauryl sulphate used is preferably 0.5 to 2 wt.% relative to the total weight of the composition.

In addition to the active substances and the lubricant, the pharmaceutical composition can also contain further usual excipients, for example antioxidants, binders, emulsifiers, colorants, fillers and disintegrants. However, in a preferred embodiment the pharmaceutical composition does not contain any further ingredients, apart from the two active substances (wherein the active substance metformin hydrochloride can be mixed with Aerosil (colloidal silica)) and the lubricant. Particularly preferably the pharmaceutical composition consists of the two active substances, Aerosil and polyethylene glycol. Alternatively the pharmaceutical composition can consist of the two active substances, optionally Aerosil, polyethylene glycol and a binder, for example polyvinylpyrrolidone (PVP; povidone).

The pharmaceutical composition can be in the form of tablets. These can preferably be obtained by direct compression or methods containing wet granulation or fusion granulation. Preferably the tablets are obtained by direct compression.

If desired, the tablets can be provided with one or a plurality of coatings, for example a film coating. Corresponding coatings are known by a person skilled in the art.

The inventor also provides a method of production of a pharmaceutical composition as described above, wherein the active substances are mixed with the lubricant and optionally further excipients and the resultant mixture is compressed to tablets, optionally after sieving and/or granulation. Preferably the mixture is not granulated prior to compression, but compressed to tablets directly. Alternatively the mixture can first be formed into granules by wet or dry granulation or fusion granulation and then compressed to tablets.

In some cases, the water content of the mixture is adjusted prior to compression to 2 to 3 wt.% relative to the total weight of the mixture. This improves the properties of the mixture, in particular for direct compression. The water content can be adjusted before or after sieving the mixture.

The accompanying Fig. 1 shows the release profiles of a pharmaceutical composition according to the invention according to example 1 for the two active substances sitagliptin and metformin in comparison with the commercial preparation Janumet®.

Fig. 2 shows the release profiles of a pharmaceutical composition according to the invention according to example 2 for the two active substances sitagliptin and metformin in comparison with the commercial preparation Janumet®.

The invention will now be explained in more detail by means of the following examples, which are not to be construed as limiting.

Example 1

Active substances and excipients	**[mg/tablet]**	**[%]**	**Initial weight [g/preparation]**
Sitagliptin phosphate monohydrate	63.13	4.79	1.26

(79.2%)			
Metformin hydrochloride (99.6%) Aerosil 0.5%	1004.02	76.23	20.08
PEG 8000	250.00	18.98	5.00

The metformin hydrochloride, as mixture with 0.5% Aerosil, was mixed with sitagliptin phosphate monohydrate and PEG for 15 minutes in a tumbling mixer at 23 rpm in the Turbula T10B. The mixture was sieved on a 0.6 mm sieve and then compressed on an eccentric press. The tablet size was 21x11 mm.

The tablets were then coated in a drum coater (Lödige LHC 25) with 0.35 wt.% of Opadry II (15 wt.% in water).

The dissolution profile of the tablets obtained was measured for the active substances sitagliptin and metformin using 900 ml of phosphate buffer, pH 6, at 37°C and 75 rpm by the paddle method (USP App. II). The dissolution profiles for the two active substances are shown in Fig. 1, wherein the dissolution profiles for the two active substances sitagliptin and metformin are shown together with the commercial product Janumet® for comparison. It can be seen that the tablets according to the invention release the active substances even more quickly than the commercial product.

Example 2

Active substances and excipients	**[mg/tablet]**	**[%]**	**Initial weight [g/preparation]**
Vildagliptin	50.45	3.87	1.01
Metformin hydrochloride (99.6%) Aerosil 0.5%	1004.02	76.97	20.08
PEG 8000	250.00	19.16	5.00

Production of the tablets was carried out as in example 1.

Example 3

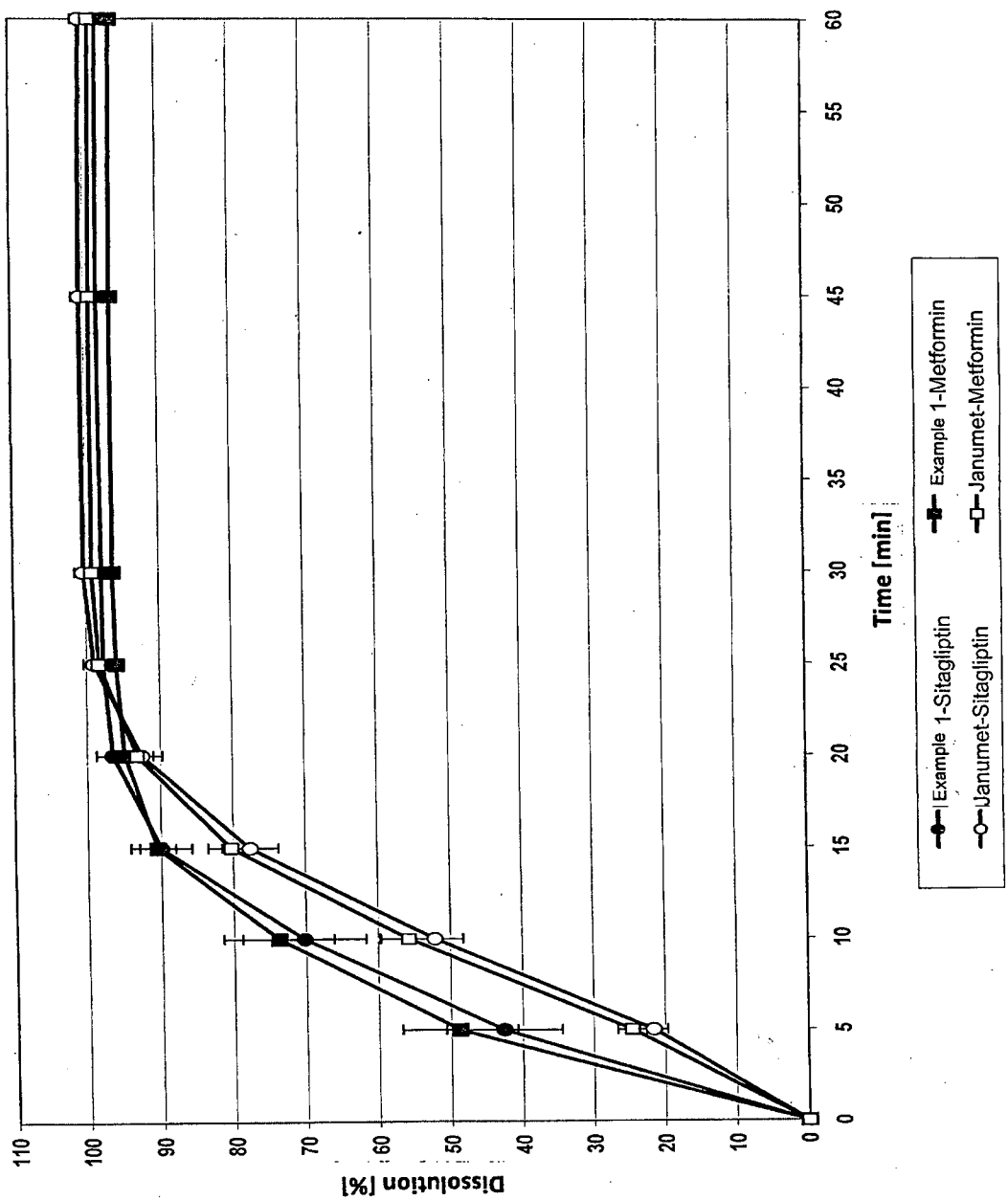
Active substances and excipients	[mg/tablet]	[%]	Initial weight [g/preparation]
Sitagliptin phosphate monohydrate (79.2%)	63.13	4.79	9.47
Metformin hydrochloride (99.6%) Aerosil 0.5%	1004.02	76.23	150.60
PEG 8000	250.00	15.18	30.00
PVP	50.00	3.80	7.50

The mixture of active substances and excipients was melted and processed to granules. The granules were compressed to tablets as in example 1.

The tablets were then coated in a drum coater (Lödige LHC 25) with 0.35 wt.% of Opadry II (15 wt.% in water).

The dissolution profiles of the tablets obtained were determined as in example 1 and are presented in Fig. 2.

Fig. 1


Dissolution [%]
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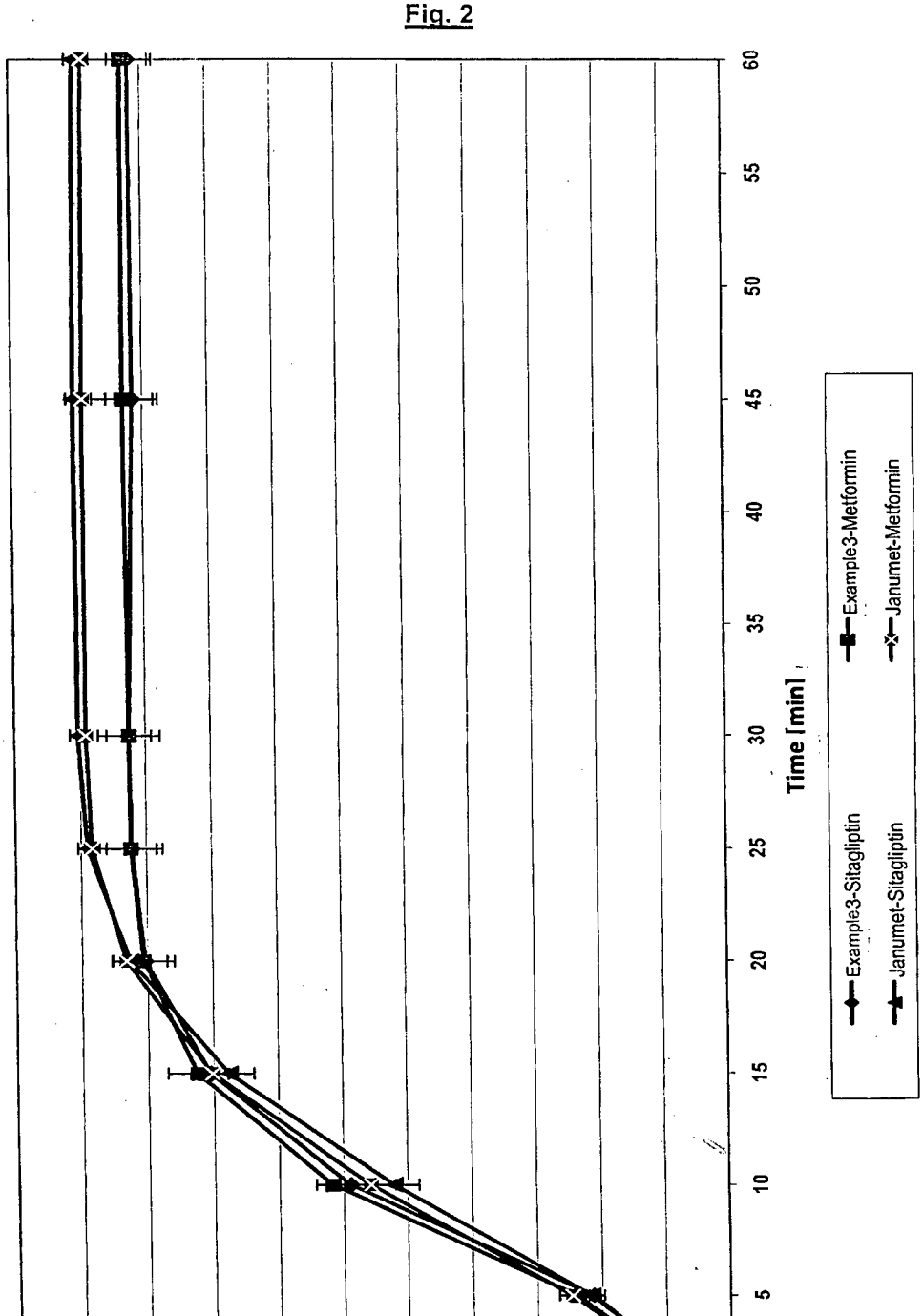
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Time [min]
Example 1-Sitagliptin
Example 1-Metformin
Janumet-Sitagliptin
Janumet-Metformin

Fig. 2


Dissolution [%]
0
10
20
30
40
50
60
70
80
90
100
110
Time [min]
0
5
10
15
20
25
30
35
40
45
50
55
60
Example3-Sitagliptin
Example3-Metformin
Janumet-Sitagliptin
Janumet-Metformin