Abstract:
The present invention relates to a pharmaceutical formulations with reduced amount of lactose, for oral intake comprising 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one hydrochloride and up to 50% of anhydrous lactose, a process for the preparation of said formulation and a method of treating chronic myeloproliferative disorder related symptoms by administering said formulation.
Improved pharmaceutical formulation

Field of the invention
The invention relates to an improved pharmaceutical 6,7-dichloro-1,5-dihydroimidazo [2,1-b]quinazolin-2(3H)-one hydrochloride composition with reduced amount of lactose, a process for preparing said composition and the use thereof for treating chronic myeloproliferative disorder related symptoms.

Background of the invention
Myeloproliferative disorders (MPDs), also known as Myeloproliferative neoplasms (MPNs) may all cause increased platelet counts. Thrombocythaemia is characterised by a sustained increase in the number of circulating blood platelets. Clinically thrombocythaemia is distinguished as a solitary finding or as occurring in association with MPNs such as polycythaemia vera (PV) chronic myeloid leukaemia (CML) and a variety of other MPNs. Where no other associated dysfunction of the bone marrow is found the condition is known as Essential Thrombocythaemia (ET).

Essential Thrombocythaemia (ET) is one of a number of chronic myeloproliferative disorders (MPD), characterised by an elevated platelet count due to an autonomous clonal proliferation of bone marrow megakaryocytes, which produce platelets. ET is associated with hyper-proliferation of megakaryocytes, with increased cell size and ploidy and a mean platelet turnover rate about six times higher than that in healthy controls.

ET is an orphan disease. It is estimated that the prevalence of ET in the EU is 2 - 3 per 10,000 persons. ET is a condition that may affect anyone at any stage of life from childhood, although the median age at diagnosis is 65 to 70 years. The female to male ratio is approximately 2:1. Up to two thirds of patients with ET are asymptomatic, and a significant number of patients are now being diagnosed as an incidental consequence of the analysis of full blood counts for other health reasons. Generally, older patients are more likely to be symptomatic at presentation, although younger patients may present with major complications. Management of ET in patients with low-risk ET is usually conservative with low-dose acetyl salicylic acid, whereas treatment of high-risk ET patients (i.e., patients older than 60 and/or with a platelet count > 1000 x 10^9/L and/or with a history of thrombo-
haemorrhagic events) is based on the use of cytoreductive therapy, with hydroxyurea (HU) as the drug of choice and interferon (INF)-alpha being reserved for young patients or pregnant women. Hydroxyurea is registered in a number of European countries for the treatment of ET. INF-alpha is used off-label for this indication, but associated with undesirable side effects. Other drugs such as busulfan are occasionally used in the management of ET patients.

Anagrelide hydrochloride (also referred to as anagrelide or anagrelide hydrochloride monohydrate) is an imidazoquinoxaline originally developed as an inhibitor of platelet aggregation, but subsequently found to have value as a platelet-lowering agent for the treatment of patients suffering from Essential Thrombocythaemia (ET), or overproduction of blood platelets. Anagrelide blocks the development and growth of megakaryocytes thereby reducing the platelet count in the blood.

Two anagrelide products that are currently on the European market are Xagrid® and Thromboreductin®. Xagrid® is an immediate release capsule which releases more than 90% of its active in vitro within the first 10 minutes and wherein anagrelide levels can be measured in the plasma of a patient within a few minutes after administration. Xagrid® is approved for the EU in 2001 for second line treatment for patients with ET. Thromboreductin® is the subject of in EP 2367539B. This document indicates that preclinical and clinical studies of pharmacologic aspects of anagrelide raise important questions regarding its mode of action and safety profile. Anagrelide dosing may cause side effects such as headache, dizziness and palpitations, and a correlation with high plasma levels of anagrelide is suggested in said patent. Especially in view of better tolerability and reduction of the negative side effects EP’539 aims to provide a medicament that is of non-immediate release resulting in a delayed but more constant supply with anagrelide. This delayed absorption rate of anagrelide will be associated with reduced peak and overall plasma levels of anagrelide and consequently markedly lower side effects will be expected. Such improved release properties would be specifically useful for the first line treatment of essential thrombocythaemia, but can also be used for second line treatment.

EP 2367539B teaches that advantageous non-immediate release characteristics resulting in reduced peak plasma levels (Cmax) can be obtained by reducing the anagrelide
particle size and by using at least 60 mg lactose monohydrate in the formulation. The recommended starting dosage of anagrelide is 1 mg/day, which should be administered orally in two divided doses (0.5 mg/dose). The recommended maximum daily dose should not exceed 5 mg.

Both currently marketed products are hard capsules containing 0.5 mg anagrelide. As additional excipient, both formulations comprise lactose, in particular one Xagrid® capsule comprises a combination of lactose monohydrate (53.7 mg) and anhydrous lactose (65.8 mg), whereas Thromboreductin® comprises lactose only in the monohydrate form (93.9 mg).

In cases, where patients require the maximal indicated daily dosage of 5 mg anagrelide, said patients are faced with a daily intake of up to approximately 1 gram of lactose. With the current products that are available in the market, difficulties with tolerability are reported due to the side effects such as headache, palpitations and diarrhoea. The presence of lactose may be the sole cause or/and exacerbate the diarrhoea. The use of additional supplements are sometimes prescribed.

Lactose tolerance varies widely among individuals with lactose maldigestion. A single threshold of lactose for all lactose intolerant subjects cannot be determined owing to the great variation in individual tolerances (European Food Safety Authority; Scientific opinion on lactose thresholds in lactose intolerance and galactosaemia; EFSA Journal 2010;8(9);1777). Hence, any reduction in lactose is considered to be beneficial to patients with lactose intolerance.

**Summary of the invention**

It is an object of the present invention to provide improved compositions of anagrelide with non-immediate release and reduced lactose content, which can be used for the treatment of chronic myeloproliferative disorder related symptoms such as essential thrombocythaemia or thrombocythaemia related to polycythaemia vera (PV), chronic myeloid leukaemia (CML), myelofibrosis or myelodysplasia or myeloproliferative neoplasms of unspecified cause.

When addressing this problem, the present inventors have unexpectedly found that
although the prior art teaches to use at least 60 mg lactose in the monohydrate form in a 0.5 mg unit dose, in order to obtain a reduced Cmax and hence reduce the side effects, the use of lactose specifically in the anhydrous form also resulted in the beneficial reduced Cmax. Even more surprisingly, when using lactose in the anhydrous form, the amount of lactose can be reduced to less than 50% when compared to the products currently available in the market. Therefore, anagrelide formulations according to the present invention can be used for the existing indications with better acceptance for patients with lactose intolerance.

Thus, in a first aspect, the present invention concerns a solid oral pharmaceutical formulation comprising anagrelide as active ingredient and between 1 to 50% of lactose, based on the total weight of the formulation, wherein said lactose is solely in the anhydrous form.

In the context of the present invention, the term "anagrelide" encompasses pharmaceutically acceptable salts, hydrates and/or solvates thereof such as anagrelide hydrochloride or anagrelide hydrochloride monohydrate.

In a preferred embodiment of the pharmaceutical formulation according to the invention, anagrelide is present in micronized form. For the present invention, micronized anagrelide means that at least 90% of the anagrelide particles are smaller than 10 µ in diameter.

In a preferred embodiment the pharmaceutical formulation according to the invention is a tablet. In one embodiment said tablet is breakable. For the indication of chronic myeloproliferative disorder related symptoms such as for example ET, this is especially advantageous, since the final dose to be given should be titrated for each patient and may lead to the use of only part of the tablet.

In yet another embodiment the pharmaceutical formulation according to the present invention further comprises a binder, a filler, a disintegrant and/or a lubricant. Preferably the binder is povidone, preferably the filler is microcrystalline cellulose, preferably the disintegrant is crospovidone, preferably the lubricant is magnesium stearate.
In yet another aspect, the present invention concerns a solid oral pharmaceutical formulation comprising:

i. 0.45 to 0.65 wt.% anagrelide hydrochloride

ii. 1 to 50 wt.% lactose anhydrous

iii. 1 to 5 wt.% binder

iv. 30 to 60 wt.% filler

v. 1 to 5 wt.% disintegrant

vi. 0.2 to 1 wt.% lubricant.

The weight percentages (wt.%) are based on the total weight of the formulation.

In yet another aspect, the present invention provides a process for the preparation of a solid oral pharmaceutical formulation comprising anagrelide comprising:

i. dry mixing a composition comprising anagrelide and lactose solely in its anhydrous form to form a blend;

ii. direct compression of the resulting blend to form a tablet.

The invention also concerns a solid oral pharmaceutical formulation obtainable by said process.

In yet another aspect, the invention concerns the solid oral pharmaceutical formulation according to the present invention for use in treating chronic myeloproliferative disorder related symptoms. This aspect of the invention may also be worded as the use of anagrelide for the manufacture of a solid oral pharmaceutical formulation according to the present invention for treating chronic myeloproliferative disorder related symptoms. In other words, this aspect of the invention relates to a method of treating chronic myeloproliferative disorder related symptoms, comprising administering to a subject in need thereof the solid oral pharmaceutical formulation according to the present invention. In one embodiment, the chronic myeloproliferative disorder related symptoms is essential thrombocythaemia. In yet another embodiment, the chronic myeloproliferative disorder related symptoms is essential thrombocythaemia, thrombocythaemia related to polycythaemia vera, chronic myeloid leukaemia, myelofibrosis or myelodysplasia or myeloproliferative neoplasms of unspecified cause.
Detailed description of the invention

The present invention provides an anagrelide formulation which comprises reduced lactose content and at the same time confers Cmax values that allows treatment of ET especially in lactose intolerant patients.

Hence, in a first embodiment, a solid oral pharmaceutical formulation comprising anagrelide as active ingredient and between 1 to 50% of lactose, based on the total weight of the formulation, wherein said lactose is used solely in the anhydrous form is provided.

The inventors surprisingly have found that by employing lactose solely in its anhydrous form, an anagrelide pharmaceutical formulation can be manufactured comprising less lactose than the formulations currently available in the market. The use of anhydrous lactose is contrary to the teaching in EP 2367539B which explicitly teaches to use lactose in its monohydrate form in order to obtain reduced maximum serum levels (Cmax) which are beneficial since this leads to less side effects. When using lactose monohydrate, EP539 also teaches to use lactose in amounts of at least 60 mg. The present invention has a similar advantageous Cmax value - and thus lower than direct release product (known as Xagrid® or Agrylin® ) that is beneficial to patients and is particularly advantageous in the treatment of ET in patients that are lactose intolerant since it has reduced lactose content of at least 50% when compared to the currently marketed products.

The formulation of the present invention comprises anhydrous lactose. For the present invention, anhydrous lactose means lactose without water, for example when water of hydration and/or crystallisation has been removed. Alternatively anhydrous lactose is also described as 0-P-D-galactopyranosyl-(1→4)-P-D-glucopyranose or as a mixture of 0-β-D-galactopyranosyl-(1→4)-a-D-glucopyranose and 0-β-D-galacto-pyranosyl-(1→4)-β-D-glucopyranose (Ph. Eur.). Alternatively, anhydrous lactose is described as primarily β-lactose or as a mixture of α- and β-lactose (USP-NF). Anhydrous lactose is known in the art and commercially available. A suitable example of anhydrous lactose is SuperTab 21AN®.

The formulation of the present invention comprises between 1 to maximal 50% of
anhydrous lactose, based on the total weight of the formulation. For example, the anhydrous lactose can be present in an amount of 1% or more, 5% or more, 10% or more, or 20% or more, or in an amount of 45% or less, 40% or less, or 30% or less based on total weight of the formulation. In certain embodiments, the anhydrous lactose is present in an amount of less than 45% based on total weight of the formulation.

In the present invention, no lactose monohydrate is used as excipient.

The term anagrelide is used for the active compound 6,7-dichloro-1,5-dihydroimidazo[2,1-b]quinazolin-2(3H)-one hydrochloride and also for 6,7-dichloro-1,5-dihydroimidazo[2, 1-b]quinazolin-2(3H)-one monohydrochloride monohydrate. Specifically, 6,7-dichloro-1,5-dihydroimidazo[2, 1-b]quinazolin-2(3H)-one monohydrochloride monohydrate is used in the present solid oral pharmaceutical formulation. In one embodiment, anagrelide is used in its micronized form which for the purpose of the present invention means that at least 90% of the anagrelide particles are smaller than 10 µm in diameter.

The amount of anagrelide per unit dose, preferably per tablet, may vary. In one embodiment, the amount of anagrelide as free base varies from about 0.5 mg to about 2.0 mg per unit dose. In one embodiment the amount of anagrelide as free base is about 0.5 mg per unit dose, preferably 0.5 mg ± 10%. In one embodiment the amount of anagrelide as free base is about 1.0 mg per unit dose, preferably 1.0 mg ± 10%. In one embodiment the amount of anagrelide as free base is about 1.5 mg per unit dose, preferably 1.5 mg ± 10%. In one embodiment the amount of anagrelide as free base is about 2.0 mg per unit dose, preferably 2.0 mg ± 10%.

The formulation of the present invention comprises a tablet. The use of a tablet is highly advantageous since for proper treatment the dosage should be determined and controlled individually by the physician. This requires titration of the dose to achieve the lowest effective dose required to reduce and/or maintain the platelet count to the required level. Hence, the tablet of the invention may contain a break line so that the tablet can be divided into equal smaller doses. This is an unmet need in the current market that only provides capsules which cannot easily be divided for proper titration.
According to yet another embodiment the formulation according to the present invention further comprises at least a binder, a filler, a disintegrant or a lubricant or a combination of two or more of these.

Suitable binders include but are not limited to povidone, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC), ethyl cellulose, sodium carboxymethyl cellulose/xylitol, starch, and the like. In a preferred embodiment the formulation according to the invention comprises povidone as a binder. Any suitable amount of binder can be employed to prepare the present pharmaceutical formulation. For example, the binder can be present in an amount of 1% or more, 2% or more, or in an amount of 5% or less, about 4% or less, based on total weight of the formulation. In a preferred embodiment, the binder is present in an amount of 1% to 5% based on total weight of the formulation.

Suitable fillers include but are not limited to microcrystalline cellulose, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, fructose, lactitol, mannitol, sucrose, xylitol, sorbitol, talc, calcium carbonate, calcium sulphate, tricalcium phosphate. In a preferred embodiment the formulation according to the invention comprises microcrystalline cellulose as a filler.

Any suitable amount of filler can be employed to prepare the present pharmaceutical formulation. For example, the filler can be present in an amount of 30% or more, 40% or more, or in an amount of 60% or less, 50% or less, based on total weight of the formulation. In a preferred embodiment, the filler is present in an amount of 30% to about 60% based on total weight of the formulation.

Suitable disintegrants include but are not limited to crospovidone, croscarmellose sodium, pregelatinized starch or sodium starch glycolate. In a preferred embodiment the formulation according to the invention comprises crospovidone as a disintegrant.

Any suitable amount of the disintegrant can be employed to prepare the present pharmaceutical formulation. For example, the disintegrant can be present in an amount of 1% or more, 2% or more, or in an amount of 5% or less, 4% or less, based on total weight of the formulation. In a preferred embodiment, the disintegrant is present in an amount of
1% to about 5% based on total weight of the formulation.

The precise identity of the lubricant present in the composition of the present invention is not critical and may be chosen from magnesium stearate or stearic acid and the like.

The lubricant can be present in any suitable amount. For example in an amount of 0.1% or more, 0.3% or more, or in an amount of 1.0% or less, 0.6% or less, based on total weight of the formulation. In a preferred embodiment, the lubricant is present in an amount of 0.1% to about 1.0% based on total weight of the formulation.

Suitably, also other excipients that are appropriate for the chosen dosage form may be present. These excipients include but are not limited to coatings, colours, flavours, glidants, retardants, spherisation aids etcetera. Some excipients present in the formulation according to the invention may have multiple functions.

In a preferred embodiment, the present invention concerns a solid oral pharmaceutical formulation comprising anagrelide, anhydrous lactose, a binder, a filler, a disintegrant and a lubricant. Preferably, the formulation comprises:

i. 0.45 to 0.65 wt.% anagrelide hydrochloride

ii. 20 to 50 wt.% lactose anhydrous

iii. 1 to 5 wt.% binder

iv. 30 to 60 wt.% filler

v. 1 to 5 wt.% disintegrant

vi. 0.2 to 1 wt.% lubricant,

wherein wt.% is based on the total weight of the formulation.

According to one embodiment of the invention, the pharmaceutical formulation is a solid oral dosage form. In a preferred embodiment, the solid oral dosage form is in the form of a tablet, a mini tablet, a caplet, a capsule or a multiparticulate such as a granulate, a pellet or a bead. In a preferred embodiment, the solid oral dosage form is a tablet.

Tablets may be prepared by techniques known in the art, such as for example by direct compression, or alternatively by association of a multiparticulate such as for example
granules and further compression into tablets.

In yet another embodiment the solid oral pharmaceutical formulation according to the invention is in the form of a multiparticulate which may be encapsulated into capsules or alternatively the multiparticulate may be packaged in a sachet or stick pack.

In one embodiment, the formulation of the invention, in particular the tablet, is obtainable by the process as described here below.

In yet another aspect, the present invention concerns a process for the preparation of a solid oral pharmaceutical formulation comprising anagrelide:

i. dry mixing a composition comprising anagrelide hydrochloride and lactose solely in its anhydrous form and one or more of to form a blend;

ii. direct compression of the resulting blend to form a tablet.

In a preferred embodiment, the process comprises dry mixing the anagrelide hydrochloride, anhydrous lactose and a binder, a filler and a disintegrant. In the process methods and standard equipment known in the art can be used. The resulting blend is tabletted using techniques and equipment commonly known in the art.

In a preferred embodiment of the present solid oral pharmaceutical formulation, the release of the active ingredient is immediate. In another preferred embodiment of the present solid oral pharmaceutical formulation, the release of the active ingredient is modified or is controlled such as sustained release or delayed release or prolonged release.

In yet another preferred embodiment of the invention, the solid oral dosage form provides a dissolution of at least 80% of the active ingredient after 30 minutes when measured using USP dissolution apparatus II (paddle) using 75 rpm, with 900 ml dissolution medium of 0.1 N HCl (pH 1.2) at 37°C.

The present invention also concerns the use of anagrelide and 1 to 50 % based on total weight of the formulation anhydrous lactose for the manufacture of a solid oral pharmaceutical formulation for treating chronic myeloproliferative disorder related symptoms, preferably for treating essential thrombocythaemia or for treating
thrombocythaemia related to polycythaemia vera, chronic myeloid leukaemia, myelofibrosis or myelodysplasia or myeloproliferative neoplasms of unspecified cause.

For the purpose of the present invention, treating essential thrombocythaemia means the reduction of elevated platelet counts in essential thrombocythaemia (ET) patients. In one embodiment, the present invention concerns the use of anagrelide and 1 to 50 % based on total weight of the formulation anhydrous lactose for the manufacture of a solid oral pharmaceutical formulation for second line treatment of chronic myeloproliferative disorder related symptoms, preferably for second line treatment essential thrombocythaemia. Second line treatment of essential thrombocythaemia means the reduction of elevated platelet counts in essential thrombocythaemia (ET) patients who are intolerant to a first line treatment, or whose elevated platelet counts are not reduced to an acceptable level by a first line treatment, in particular ET patients who are intolerant their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

Especially in view of its reduced lactose content, the formulation according to the present invention is better tolerated by lactose intolerant patients.

The examples described herein are illustrative of the present invention and are not intended to be limitations thereon.

EXAMPLES

Example 1: Preparation of tablet batches comprising anhydrous lactose

Anagrelide hydrochloride monohydrate in amounts indicated in Table 1, microcrystalline cellulose, crospovidone and povidone were sifted and added to a high shear granulator. The material was mixed for 5 minutes and subsequently loaded into a bin blender. Sifted mg-stearate was added and the material was blended for 4 minutes. The obtained blend was transferred to Korch compression machine and circular 6.5 mm anagrelide tablets (0.5 mg) were prepared. Dose proportional 1 mg tablets were prepared similarly, and tableted into circular 9.0 mm tablets.
Table 1: Formulation of anagrelide tablets according to the invention versus the comparative composition Thromboreductin®

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation of the invention</th>
<th>Comparative Thromboreductin ® (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anagrelide hydrochloride</td>
<td>0.61</td>
<td>0.57</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>44.39</td>
<td>x</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>x</td>
<td>93.9</td>
</tr>
<tr>
<td>Povidone</td>
<td>2.00</td>
<td>6.0</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>50.00</td>
<td>22.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>2.50</td>
<td>5.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.50</td>
<td>1.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100.0</td>
<td>129.97</td>
</tr>
</tbody>
</table>

The formulation according to the invention comprises only 47% of the lactose compared to Thromboreductin®.

Example 2: Pharmacokinetic study

A randomized, balanced, open-label, single dose, crossover comparative bioavailability study of tablets according to the invention comprising anagrelide 1 mg and comparative Thromboreductin® 2 x 0.5 mg capsules from AOP Orphan Pharmaceuticals, Austria, in healthy adult subjects under fasting conditions. A total number of 42 subjects were randomised and received medication. In each period of the study, subjects were housed (check-in) in the clinical unit of the study center at least 12 hours before dosing and until 8 hours after drug administration (check-out). All subjects had overnight fasting of at least 10 hours prior to drug administration and 4 hours after dosing. Subjects were in a sitting posture during dosing. As per the randomization schedule, the subjects were administered a single dose of anagrelide formulation according to the invention or the comparative formulation Thromboreductin® under fasting condition with 240 ± 2 mL of water. After dosing, subjects were advised to remain upright for the first 2 hours. The drug was administered by trained study personnel under supervision of the investigator.

After a washout of at least 7 days, there was a crossover to another treatment. During course of the study, safety parameters assessed were vital signs (blood pressure, pulse rate, and oral temperature) performed at 0.00 hours and post-dose at 2.00, 4.00, 6.00
and 8.00 hours. Pre dose vitals were measured within 1 hour prior to dosing. A variation of +30 minutes during in-house vital check was acceptable. For safety of the subjects, physical examination was performed at the pre-study screening, on the day of check-in and before the check-out in all three periods.

Forty one (41) subjects completed all study periods according to the protocol. Hence, for comparative pharmacokinetic and statistical analysis 41 subjects were considered. For the safety analysis, all 42 subjects met the criteria of the safety population. Maximum plasma concentration (Cmax) and area under the curve (AUC 0-t) of anagrelide was measured by using a validated analytical LC-MS/MS method. Ln-transformed pharmacokinetic parameters AUC 0-t and Cmax were evaluated statistically using the Proc GLM procedure of SAS®. The F test was performed to determine the statistical significance of the effects involved in the model with a 5% level of significance (p=0.05).

The results from the comparative statistical evaluation of the bioavailability of the formulation of the invention compared to the Thromboreductin® preparation are presented in Table 2.

Table 2. Pharmacokinetic parameters for Anagrelide tablet of the invention and Thromboreductin® capsule (Comparative)

<table>
<thead>
<tr>
<th>PK Variable</th>
<th>Formulation of the invention</th>
<th>Thromboreductin® formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (pg/mL)</td>
<td>6080.5</td>
<td>6150.11</td>
</tr>
<tr>
<td>AUC0-t (pg.hr/mL)</td>
<td>16115.94</td>
<td>15846.28</td>
</tr>
</tbody>
</table>

From this study it was concluded that with the formulation according to the invention similar low plasma levels and hence similar safety profile could be reached when compared to Thromboreductin® product.
Claims

1. A solid oral pharmaceutical formulation comprising anagrelide as active ingredient and between 1 to 50% lactose, based on total weight of the formulation, wherein said lactose is solely in the anhydrous form.

2. The pharmaceutical formulation according to claim 1, wherein the anagrelide is present in micronized form.

3. The pharmaceutical formulation according to claim 1 or 2, which is a tablet.

4. The pharmaceutical formulation according to any one of claim 1 - 3, further comprising a binder, a filler, a disintegrant or a lubricant or a combination of two or more of these.

5. The pharmaceutical formulation according to claim 4 comprising
   i. 0.45 to 0.65 wt.% anagrelide hydrochloride
   ii. 1 to 50 wt.% lactose anhydrous
   iii. 1 to 5 wt.% binder
   iv. 30 to 60 wt.% filler
   v. 1 to 5 wt.% disintegrant
   vi. 0.2 to 1 wt.% of lubricant
   wherein wt.% is based on total weight of the formulation.

6. The pharmaceutical formulation according to claim 4 or 5, wherein the binder is povidone and/or the filler is microcrystalline cellulose and/or the disintegrant is crospovidone.

7. A process for the preparation of the solid oral pharmaceutical formulation according to any one of claims 1 - 6, comprising
   i. dry mixing a composition comprising anagrelide hydrochloride and lactose solely in its anhydrous form, to form a blend;
   ii. direct compression of the resulting blend to form a tablet.
8. The pharmaceutical formulation according to any one of claims 1 - 6, which is obtainable by the process according to claim 7.

9. The solid oral pharmaceutical formulation according to any one of claims 1 - 6 and 8, for use in treating chronic myeloproliferative disorder related symptoms.

10. The solid oral pharmaceutical formulation for use according to claim 9, wherein the chronic myeloproliferative disorder related symptoms is essential thrombocythaemia, thrombocythaemia related to polycythaemia vera, chronic myeloid leukaemia, myelofibrosis or myelodysplasia or myeloproliferative neoplasms of unspecified cause.

11. The solid oral pharmaceutical formulation according to any one of claims 1 - 6 and 8, for use in treating essential thrombocythaemia, thrombocythaemia related to polycythaemia vera, chronic myeloid leukaemia, myelofibrosis or myelodysplasia or myeloproliferative neoplasms of unspecified cause.
### INTERNATIONAL SEARCH REPORT

**International application No:** PCT/EP2016/025052

#### A. CLASSIFICATION OF SUBJECT MATTER

|------|----------|------------|------------|------------|------------|

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

<table>
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<td>X</td>
<td>WO 2008/090569 AI (PANACEA BIOTEC LTD) [IN]; JAIN RAJESH [IN]; JINDAL KOUR CHAND [IN]; BOL 31 July 2008 (2008-07-31) example 8</td>
<td>1-4,7-11</td>
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Y

US 2005/008704 AI (RAY ANUP KUMAR [US] ET AL) 13 January 2005 (2005-01-13) paragraphs [0028], [0044]; claims 7,8; figure 1; example 10

Y


A


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

**X** See patent family annex.

* Special categories of cited documents:

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

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*"Z"* document member of the same patent family

Date of the actual completion of the international search: 25 July 2016

Date of mailing of the international search report: 04/08/2016

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Authorized officer:

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Form PCT/ISA/210 (second sheet) (April 2005)
<table>
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