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Methods and Compositions.

(57)

The present invention relates to methods for and of treating, ameliorating or preventing colorectal cancer (CRC) in humans using polyethylene glycol (PEG) or a PEG block-copolymer such as Pluronic® F68. Compositions for use in treating, ameliorating and/or preventing CRC comprising PEG are also disclosed. Such compositions may be used in the methods of the invention.

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Dit octrooi is verleend ongeacht het bijgevoegde resultaat van het onderzoek naar de stand van de techniek en schriftelijke opinie. Het octrooischrift wijkt af van de oorspronkelijk ingediende stukken. Alle ingediende stukken kunnen bij NL Octrooicentrum worden ingezien.

Methods and Compositions

5 The present invention concerns methods of and for the treatment, amelioration and/or prevention of colorectal cancer (CRC) in humans. The present invention also concerns compositions for use in such methods.

10 Colorectal cancer is a major cause of death in the human population, particularly in North America and Europe. Prevention is urgently required and therefore research into various strategies including control of diet and other lifestyle modifications, including chemical interventions, has been reported.

15 In International Patent Application No: WO00/24407, the use of a non-fermented osmotic laxative such as polyethylene glycol (PEG) to treat and prevent colorectal cancer is disclosed. This finding was based on work carried out in an azoxymethane (AOM) model of colon cancer in Fischer F344 rats. It suggests that the doses used in rats may be translated into a daily dose in humans of between 10 to 80g. However, no direct evidence is disclosed that a therapeutic effect for PEG exists in human forms of CRC nor over what timeframe such an exposure is necessary to achieve such an effect.

20 Dorval E. *et al*; Gastro Clin Biol, 30:1196-1199 (2006), investigated, in a human population based study, the prevalence of colorectal adenomas in association with dietary PEG consumption. Consecutive patients, attending hospital for routine total colonoscopy, were asked if they had previously taken a laxative or a non-steroidal anti-inflammatory drug (NSAID). Based on the answers provided, the authors concluded that use of Forlax[®], a PEG containing bowel preparation, was associated with a lower incidence of colorectal tumours, yet other PEG or PEG-like laxatives including MOVICOL[®], Transipeg[®] and Idrocol[®] did not produce significant results. The authors posited that one reason may have been that the "PEG dose varies from one brand to another, and appears to be among the highest in Forlax[®]. As noted in the paper, since the

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study was based on a patient based questionnaire, “this survey did not yield reliable information regarding the duration, quantity, regularity or timing of PEG ingestion.”

5 In addition to the above-noted references, there have been other studies involving rodents building on the work mentioned above, which generally tend to the view that a relatively high dose of a PEG in a relatively short time frame can reduce incidences of ACF and EGFR - believed to be markers for colon cancer. There is no apparent consensus regarding the timing of the administration of the PEG in order to be effective in reduction of the surrogate marker(s) and the level of dose of the PEG, if scaled up for human use, 10 would result in diarrhoea. The requirement for a high dose is echoed in the Dorval (2006) reference, which shows, at table II, that MOVICOL® (a PEG plus electrolytes composition) is ineffective; similarly, it shows that the combined results of PEG-containing laxatives are not significant. To date, this appears to be the only published study related to the human use of PEG in the context of colorectal cancer, yet it does not 15 exclude data from patients whose constipation (and the reason for them taking a laxative such as Forlax® or MOVICOL®) is caused by, or is a symptom of, colorectal cancer.

Surprisingly, when the present inventors instigated a study of a General Practice Research Database (GPRD) to describe the incidences of colorectal cancer in the human population 20 following different types of laxative exposure by comparison with controls sampled from the same laxative cohort population but having no diagnosis of colorectal cancer, they found a potential dose-response relationship in patients ingesting over 60 sachets of MOVICOL®, both 24 and 36 months prior to the earliest date they presented with evidence of a CRC diagnosis. MOVICOL is provided in a sachet containing 13.8g 25 powder for making up into an oral solution. Each sachet contains: 13.1250g Macrogol (polyethylene glycol (PEG)) 3350, 0.3507g sodium chloride, 0.1785g sodium bicarbonate and 0.0466g potassium chloride. This is the standard dose of MOVICOL. It also contains flavouring and sweetener. MOVICOL has been on the market since 1995.

30 Therefore, in accordance with the present invention there is provided a composition for use in a method for treating, ameliorating and/or preventing CRC in a human comprising

administering to the human approximately 800 grams or greater (e.g. 2362 grams or greater) of PEG or PEG block co-polymer over a period of 36 consecutive calendar months.

- 5 In accordance with the present invention there is provided a composition for use in a method for treating, ameliorating and/or preventing CRC in a human comprising administering to the human approximately 800 grams or greater (e.g. 2362 grams or greater) of PEG or PEG block co-polymer over a period of 24 consecutive calendar months.

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In accordance with the present invention there is provided a composition for use in a method for treating, ameliorating and/or preventing CRC in a human comprising administering to the human an effective and sub-laxative amount of a PEG or PEG block co-polymer.

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In one aspect of the invention the composition of the invention is for use in treating CRC in a human. In another aspect, the composition of the invention is for ameliorating CRC in a human. In a further aspect, the composition of the invention is for use in preventing CRC in a human.

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In another aspect of the invention, there is provided a method of treating, ameliorating and/or preventing colorectal cancer (CRC) in a human which method comprises administering to the human an effective and sub-laxative dose of PEG or PEG block co-polymer.

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In another aspect of the invention there is provided a method for treating, ameliorating and/or preventing CRC in a human which method comprises administering to the human an effective amount and sub-laxative dose of PEG or PEG block co-polymer.

In another aspect of the invention there is provided a method; (a) for preventing constipation and; (b) of preventing CRC in a human which method comprises administering an effective and sub-laxative dose of PEG or PEG block co-polymer.

- 5 In another aspect of the invention there is provided a method; (a) for preventing constipation and; (b) for preventing CRC in a human which method comprises administering an effective and sub-laxative dose of PEG or PEG block co-polymer.

- 10 In another aspect of the invention there is provided a method; (a) for preventing constipation and; (b) for ameliorating CRC in a human which method comprises administering to the human an effective and sub-laxative dose of PEG or PEG block co-polymer.

- 15 In another aspect of the invention there is provided a method; (a) for preventing constipation and; (b) for treating CRC in a human which method comprises administering to the human an effective and sub-laxative dose of PEG or PEG block co-polymer

- 20 In another aspect, there is provided a composition suitable for human administration comprising, as a unit dose, a sub-laxative amount of PEG or PEG block co-polymer.

- In another aspect, there is provided a composition for use in a method of the invention described *supra* comprising, as a unit dose, a sub-laxative amount of PEG or PEG block co-polymer.

- 25 The term “sub-laxative amount” means an amount that does not increase the average number of stools per week for the human subject concerned.

- 30 The term “sub-laxative dose”, means a dose that does not increase the average number of stools per week for the human subject concerned.

The term “PEG” means polyethylene glycol having the general formula $H-(O-CH_2-CH_2)_n-OH$.

5 The term “PEG block co-polymer” refers to a co-polymer of polyethyleneglycol with polypropylene glycol, namely, polyethylenepolypropylene glycol. Exemplary PEG block co-polymers include those available under the tradename “Pluronic[®] F68” or “poloxamer 188”.

10 The term “treating” and grammatical variations thereof is intended to mean that methods and compositions of the invention may be able to cure and/or reverse the normal disease course of CRC, particularly early stage colorectal pathologies associated with the development of CRC, for example by treating colon polyps.

15 The term “ameliorating” and grammatical variations thereof is intended to mean that methods and compositions of the invention can slow or stop the progression of early stage colorectal pathologies towards the development of CRC, e.g. slow or stop the further development of colon polyps and/or aberrant crypt foci (ACF) into CRC.

20 The term “preventing” and grammatical variations thereof is intended to mean that methods and compositions of the invention reduce the risk of developing CRC and/or (as the case may be) constipation.

25 The term “colorectal cancer” or “CRC” refers to colorectal, colon and/or rectal cancer in humans.

The term “one month” means a contiguous 30 day period.

The phrase “a method for” is intended to denote a purposive method.

30 In certain embodiments of the invention described *supra*, a dose (e.g. effective and sub-laxative dose) is administered to provide approximately 800 grams or greater (e.g. 2362

grams or greater) of PEG or PEG block co-polymer over a period of 36 consecutive calendar months. In certain other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide between 800 and 2365 (e.g. 800.6 to 2362.5) grams of PEG or PEG block co-polymer over a period of 36
5 consecutive calendar months.

In certain embodiments of the invention described *supra*, a dose (e.g. effective and sub-laxative dose) is administered to provide approximately 800 grams or greater (e.g. 2362 grams or greater) of PEG or PEG block co-polymer over a period of 24 consecutive
10 calendar months. In certain other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide between 800 and 2365 (e.g. 800.6 to 2362.5) grams of PEG or PEG block co-polymer over a period of 24 consecutive calendar months.

15 In other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide 266 grams or greater (e.g. 400 grams or greater; 787 grams or greater; 1181 grams or greater) of PEG or PEG block co-polymer over a period of 12 consecutive calendar months. In certain embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to
20 provide between 266 grams and 1181 grams (e.g. between 266.9 grams and 787.5 grams; between 400.3 grams and 1181.3 grams; between 400.3 grams and 787.5 grams) of PEG or PEG block co-polymer over a period of 12 consecutive calendar months.

In other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide 22 grams or greater (e.g. 33 grams or greater; 65 grams or greater; 98 grams or greater) of PEG or PEG block co-polymer over a period of one month. In certain embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide between 22.2 grams and 98.4 grams (e.g. between 33.3 grams and 98.4 grams; 22.2 grams and 65.6 grams; 65.6 grams
25 and 98.4 grams) of PEG or PEG block co-polymer over a period of one month.
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In other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide 5.1 grams or greater (e.g. 7.7 grams or greater; 15.1 grams or greater; 22.7 grams or greater) of PEG or PEG block co-polymer over a period of one week. In certain embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide between 5.1 grams and 22.7 grams (e.g. between 7.7 grams and 22.7 grams; 5.1 grams and 15.1 grams; 15.1 grams and 22.7 grams) of PEG or PEG block co-polymer over a period of one week.

In other embodiments of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide 0.73 grams or greater (e.g. 1.1 grams or greater; 2.2 grams or greater; 3.2 grams or greater) of PEG or PEG block co-polymer over a period of one day. In certain embodiments of methods of the invention described *supra*, a dose (e.g. an effective and sub-laxative dose) is administered to provide between 0.73 grams and 3.22 grams (e.g. between 1.1 grams and 3.2 grams; 0.73 grams and 2.2 grams; 2.2 grams to 3.2 grams) of PEG or PEG block co-polymer over a period of one day. Such doses may be administered daily over period of 24 or 36 consecutive calendar months. Alternatively, such doses may be administered intermittently over a period of 24 or 36 consecutive calendar months.

In all embodiments described herein, it will be apparent to the reader of this specification that ranges specified as being “between” or “within” two values are to be understood as being inclusive of those values, for example “between 1.1 grams and 3.2 grams” includes 1.1 grams and 3.2 grams respectively.

In other embodiments of the invention, compositions for use in a method (such as the methods described *supra*) for treating, ameliorating and/or preventing CRC in humans comprising an amount (e.g. effective and sub-laxative) of a PEG or PEG block co-polymer are provided.

In certain embodiments, the composition of the invention is in the form of a tablet (e.g. chewable or suckable tablet), capsule, caplet, troche, liquid, powder (e.g. powder for

solution or suspension) and granules. Preferably, it is the form of a solid composition for oral administration. It may be a solid tablet, for example a chewable and/or suckable tablet.

In some embodiments of the invention, the PEG has an average molecular weight of at least 400, or at least 1000, or between 2000 to 10000 Daltons (e.g. 2500 to 8500, preferably 3000 to 8000 (e.g. 6000 or 8000), more preferably 2500 to 4500, e.g. 3350 or 4000). In certain embodiments, a blend of PEG molecules is provided of differing molecular weights to give a desired overall average molecular weight (for example an average molecular weight of 3350 or thereabout, or an average molecular weight of 4000 or thereabout). Exemplary PEG products are macrogol 3350, macrogol 4000, macrogol 6000, macrogol 8000 and are available commercially.

In some embodiments, the composition of the invention is for treating CRC. In some embodiments, the composition of the invention is for ameliorating CRC. In some embodiments, the composition of the invention is for preventing CRC.

Accordingly, the present invention provides a solid composition for oral administration as a solid for treating, ameliorating and/or preventing CRC comprising:

- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
- (b) 10 – 40 % w/w of a solid (sometimes referred to herein as “solid of component (b)”))

The invention provides a solid composition for oral administration as a solid for treating, ameliorating and/or preventing CRC comprising:

- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da;
- (b) 10 – 40 % w/w of a solid; and optionally
- (c) q.s. to 100% w/w of further excipients such as flavourings, sweeteners and lubricants.

Herein, “% w/w” of a component is understood to mean the proportion, as a percentage, that the weight of the respective component makes up of the total weight of the solid composition.

- 5 The present invention further provides a solid composition for oral administration as a solid for treating, ameliorating and/or preventing CRC comprising:
- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
 - (b) 10 – 40 % w/w of a solid selected from the group; sorbitol, lactose,
10 dextrates, cellulose, xylitol, maltitol, mannitol.

The present invention further provides a solid composition for oral administration as a solid for treating, ameliorating and/or preventing CRC comprising:

- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular
15 weight within the range 2,000 to 10,000 Da; and
- (b) 10 – 40 % w/w of a solid selected from the group: sorbitol, lactose, lactose and starch (e.g. a compound comprising lactose monohydrate and maize starch such as Starlac[®]), dextrates, cellulose (such as microcrystalline cellulose), xylitol, maltitol and mannitol.

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- Preferably, the solid of component (b) is greater than 10%w/w, preferably greater than 12% w/w, more preferably greater than 15% (e.g. 15% to 17%) of the solid composition. Preferably the weight ratio of component (a) to component (b) is 1.25:1 to 9:1, preferably 2:1 to 7:1, preferably 4:1 to 6:1. In preferred embodiments, the ratio of component (a) to
25 component (b) is approximately 5:1.

Preferably, the solid composition is chewable and/or suckable. It may be a solid tablet, for example a chewable and/or suckable tablet.

- 30 It has surprisingly been found that a solid composition of the invention comprising PEG component (a) and solid component (b) is pleasantly chewable or suckable, has good

taste, structural integrity and beneficial manufacturing properties. By “chewable” or “suckable” is meant herein that the solid composition is for oral administration and is capable of being chewed or sucked in the mouth so that the first step in the digestive process starts in the buccal cavity.

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Compositions of the invention may further comprise electrolytes. Compositions of the invention are preferably substantially free from electrolytes.

For example, they are preferably substantially free from sodium chloride, potassium chloride and sodium bicarbonate. They are preferably substantially free from sulphates or phosphates, for example, they are particularly preferred to be substantially free from sodium sulphate. Compositions of the invention are preferably substantially free from carbonates, bicarbonates, alkali metal ions and halide ions. Compositions of the present invention are most preferably substantially free from sodium, potassium, chloride, bicarbonate, carbonate and/or sulphate ions. In many instances, flavourings, lubricants and sweeteners may contain small amounts of electrolytes. Such amounts are not considered herein to be “substantial”. Compositions of the invention are preferably substantially free from alginates and/or ascorbates and/or citrates. By “substantially free from” herein is also meant that the ingredient is not added to the composition during preparation or manufacture.

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In some embodiments, compositions of the present invention are substantially free from any osmotic agent other than PEG or PEG block co-polymer.

The polyethylene glycol (PEG) for use in a solid composition of the invention preferably has an average molecular weight (for example a weight average molecular weight), in Daltons, within the range 2,000 to 10,000, preferably 2,500 to 8,500, preferably 3,000 to 8,000, more preferably 3,000 to 6,000, more preferably 2,500 to 6,500, more preferably 2,500 to 4,500 for example 3,000 to 4,500, for example 3,000 to 4,100, for example 3,000 to 4,000. The PEG may have an average molecular weight within the range 6,000 to 10,000, for example 7,000 to 9,000. For example, the PEG may be, or comprise PEG

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3,350, PEG 4,000 or PEG 8,000 as defined in national or regional pharmacopoeias. Further examples of suitable PEGs recognized in some national pharmacopoeias include Macrogols, for example Macrogol 4,000. Optionally, the PEG used in compositions of the invention may comprise two or more different PEG components. Optionally, the PEG used in compositions may have at least two differing average molecular weights. PEG of the relevant molecular weights in a form suitable for use in humans is available commercially.

In a preferred embodiment, PEG is present in the solid composition in an amount of 60 to 90% w/w, preferably 70 to 90% w/w, more preferably 70 to 89 % w/w, for example 75 to 89 % w/w. In a further embodiment, PEG is present in an amount of 78 to 89 % w/w, for example 80 to 85% w/w, for example 81 to 85 % w/w, for example 80 to 84 % w/w, for example 82 to 84 % w/w. In a further embodiment, PEG is present in an amount of 50 to 80% w/w, for example 60 to 80% w/w, for example 70 to 80 % w/w, for example 70 to 79% w/w, for example 75 to 79% w/w.

In some embodiments, the composition comprises between 0.1 to 6.5 grams (e.g. 0.73 grams to 3.2 grams; 1.1 grams to 3.2 grams; 0.73 grams to 2.2 grams) of PEG or PEG block co-polymer. In other embodiments, the composition comprises 5 grams or less of PEG or PEG block co-polymer. In other embodiments the composition comprises between 0.2 grams to 6.5 grams (e.g. 0.3 grams to 5.0 grams) of PEG or PEG block co-polymer. In further embodiments, the composition comprises between 1 to 4 grams of PEG or PEG block co-polymer. In other embodiments, the composition comprises between 1.5 and 2.5 grams of PEG or PEG block co-polymer. In other embodiments, the composition comprises between 2.0 grams to 2.5 grams of PEG or PEG block co-polymer, for example 2.2 grams or thereabout.

The solid of component (b) is preferably selected from the group consisting of sorbitol, lactose, lactose and starch, dextrans, cellulose (e.g. microcrystalline cellulose), xylitol, maltitol, mannitol. Lactose or similar ingredients may be present in hydrated form.

Where the solid of component (b) is lactose and starch, the lactose component may be in the form of a monohydrate. The starch component may be derived from any suitable source such as wheat starch, maize starch, potato starch and rice starch. The lactose component may make up 50% to 95% of the lactose/starch solid, for example 60% to 90%, e.g. 70 to 85% such as 85%.

Solids of component (b) are preferably of a purity and grade suitable for consumption by e.g. humans.

The solid of component (b) makes up 10 to 40 % w/w of the solid composition. In a preferred embodiment, the solid of component (b) makes up 10 to 30% w/w of the solid composition, preferably greater than 10% w/w up to (and including) 30%w/w. For example, the solid of component (b) makes up 10 to 25% w/w, for example 10 to 20% w/w, preferably 12 to 20 % w/w, more preferably 12 to 19% w/w, 12 to 18% w/w, or 12 to 17 % w/w. For example, the solid of component (b) may make up 14 to 20% w/w, 14 to 19% w/w or 14 to 18% w/w 14 to 17% w/w of the solid composition such as 15 to 16.5%w/w of the solid composition of the invention.

Preferably, the solid of component (b) is mannitol. It has been found that a solid composition comprising PEG and mannitol is more palatable than a solid composition comprising PEG and no mannitol, even if flavouring is added. In particular, it has been found that a tablet comprising PEG and mannitol has a much lower requirement for lubricant or lubrication during tablet manufacture than a tablet comprising PEG but no mannitol. A high level of a lubricant in a tablet generally makes the tablet have an unacceptable taste. The reduced level (or absence of) a lubricant as compared with a tablet comprising PEG but no mannitol brings about an improved palatability (taste and mouthfeel) of a chewable or suckable tablet comprising PEG and mannitol. Such tablets are thus particularly suitable for use in the current invention.

Typically, solid compositions of dry ingredients are manufactured using dry granulation followed by punching with punch and die equipment. In a punch and die machine, dry

ingredients are compressed together. It has surprisingly been found that a solid composition comprising PEG and mannitol in the specified proportions has better structural integrity and is more convenient to manufacture than a solid composition comprising PEG and no mannitol, or a smaller proportion of mannitol. Solid compositions of that type are less susceptible to capping and laminating during punch and die manufacture than solid compositions comprising a smaller proportion of mannitol, or no mannitol. Solid compositions that become capped or laminated during die pressing are not suitable for use and they become waste. It has been found that a solid composition containing between 50 and 90% w/w PEG and 10 to 40% w/w mannitol has better tablet pressing characteristics than a solid composition containing no mannitol or 10%w/w or less mannitol, for example less than 10% mannitol. Such compositions are thus particularly suitable for use in the current invention.

Mannitol may make up 10 to 40 % w/w of the solid composition. In a preferred embodiment, mannitol makes up 10 to 30% w/w of the solid composition. For example, mannitol makes up 10 to 25% w/w, for example 10 to 20% w/w, preferably 12 to 20 % w/w, more preferably 12 to 19% w/w, 12 to 18% w/w, or 12 to 17 % w/w. For example, mannitol may make up 14 to 20% w/w, 14 to 19% w/w or 14 to 18% w/w 14 to 17% w/w of the solid composition of the invention. Mannitol may be provided in various physical forms. For example, mannitol is available commercially in granular, powder or spray-dried form. In a preferred embodiment, the mannitol is granular. Mannitol is commercially available from several suppliers, including Merck, SPI Polyols Inc and Roquette.

In an embodiment, the PEG and mannitol are present in a weight ratio of PEG:mannitol of 1.25:1 to 9:1 (e.g. 3:1 to 9:1, or 4:1 to 9:1), preferably 2:1 to 7:1, preferably 4:1 to 6:1 or 4:1 to 8:1, for example 5:1 to 6:1. In preferred embodiments the ratio of PEG to mannitol 5:1 or thereabout.

The structural integrity of the solid composition is retained when the mannitol is granular mannitol. It is surprising that the solid composition of the invention is so structurally

sound with granular mannitol. In general it is found that granular mannitol cannot be used with concentrations of other materials exceeding 25% by weight (Handbook of Pharmaceutical Excipients, 5th Ed., Pharmaceutical Press, 2006, page 452). It has been found that solid compositions for use in the invention, which comprise 60 to 90% w/w of materials other than mannitol, are readily manufacturable and have good structural integrity.

It has also surprisingly been found that a solid composition for use in the invention, comprising PEG and mannitol in the specified proportions is less prone to sticking to punch and die equipment than a solid composition comprising PEG and a smaller proportion of mannitol, or no mannitol. This is particularly important when manufacturing compositions of the present invention at commercial scale since fouling of the manufacturing machinery may lead to manufacturing down-time with the increased costs associated therewith.

Lubricants can be included in tablet compositions to reduce the propensity for them to stick to the punch or die after die pressing. Examples of lubricants include magnesium stearate, potassium stearate, talc, stearic acid, sodium lauryl sulphate, and paraffin. Mixtures of different lubricants may be used. It has been found that a solid composition for use in the invention, comprising PEG and mannitol in the specified proportions, requires a smaller proportion of lubricant to satisfactorily avoid sticking than a tablet comprising PEG and a smaller proportion of mannitol, or no mannitol. Preferably, a solid composition comprises lubricant in an amount of 2.0% w/w or less, for example 1.5% w/w or less, or 1.0% w/w or less. For example it may comprise lubricant in an amount of 0.1 to 0.9% w/w, for example 0.2 to 0.8% w/w, preferably 0.3 to 0.7% w/w. For example, the lubricant is present in ratio of solid of component (b) (such as mannitol): lubricant ratio of 170:1 to 16:1, for example 57:1 to 20:1. A particularly preferred lubricant is magnesium stearate. If the lubricant is magnesium stearate, it is effective to satisfactorily avoid sticking when used at a level of under 1% w/w. Accordingly, in an embodiment, the tablet of the invention further comprises magnesium stearate in an amount of 0.1 to 0.9% w/w, for example 0.2 to 0.8% w/w, preferably 0.3 to 0.7% w/w,

more preferably 0.5% w/w. It is surprising that magnesium stearate is effective at these levels as, in general, magnesium stearate is required at a level of over 1% in compositions comprising mannitol (Handbook of Pharmaceutical Excipients, 5th Ed., Pharmaceutical Press, 2006, page 452).

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Thus the present invention provides a solid composition for administration as a solid for treating, ameliorating and/or preventing CRC comprising;

- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da;
- 10 (b) 10 – 40 % w/w of mannitol; and
- (c) 0.1 to 0.9% (e.g. 0.2 to 0.8%, 0.3 to 0.7% such as 0.5%) w/w of a lubricant such as magnesium stearate.

In some embodiments, the ratio of mannitol:lubricant is preferably 10:1 or greater, 15 preferably, 20:1 or greater e.g. 25:1 or greater such as 30:1 or greater (e.g. 30:1 to 35:1 such as 30.6:1 or 32.4:1).

In an embodiment, a solid composition of the invention does not include any added flavouring. In a preferred embodiment, a solid composition of the invention includes at 20 least one flavouring. Suitable flavourings are available from various flavour manufacturers and suppliers, for example International Flavours and Fragrances Inc. (Duddery Hill, Haverhill, Suffolk, CB9 8LG, United Kingdom), Ungerer & Company (Sealand Road, Chester, CH1 4LP, United Kingdom), Firmenich (Firmenich UK Ltd., Hayes Road, Southall, Middlesex, UB2 5NN, United Kingdom) or S. Black Ltd 25 (Foxholes Business Park, John Tate Road, Hertford, Herts, SG13 7YH, United Kingdom). Examples of suitable flavours include orange, lemon-lime, lemon, citrus, chocolate, tropical fruit, aloe vera, peppermint, tea, strawberry, grapefruit, blackcurrant, pineapple and vanilla, raspberry-lemon, cola flavour, and combinations thereof.

30 Preferred flavours are peppermint and raspberry-lemon flavour.

A flavouring may be integral in a solid composition, or it may be coated onto its surface. In one embodiment, the flavouring is integral in the solid composition. In such a solid composition, the flavouring preferably makes up 0.1 to 15% w/w of the solid composition. For example, the flavouring may make up 0.1 to 5% w/w of the solid composition, for example 0.1 to 2.0% w/w, for example 0.2 to 2.0% w/w. When the flavouring is peppermint, it is preferably present at a level of 0.1 to 1.0% w/w, for example 0.15 to 0.5% w/w. This level is particularly preferred when the solid of component (b) such as mannitol is present at a level of 14 to 17 % w/w of the solid composition of the invention. When the flavouring is raspberry-lemon, it is preferably present at a level of 0.5 to 2.0% w/w, for example 1.0 to 2.0%, for example 1.2 to 1.8% w/w. This level is particularly preferred when the solid of component (b) such as mannitol is present at a level of 14 to 17% w/w of the solid composition of the invention.

In an embodiment, the solid of component (b) such as mannitol and flavouring are, for example, present in a ratio of solid :flavouring of 170:1 to 3:1; when the flavouring is peppermint, the solid of component (b) such as mannitol and flavouring are preferably present in a ratio of solid :flavouring of 113:1 to 28:1. When the flavouring is raspberry-lemon, the solid of component (b) such as mannitol and flavouring are preferably present in a ratio of solid of component (b): flavouring of 14:1 to 7:1.

A solid composition of the invention may comprise one or more sweeteners. Sweeteners may be sugar-based. Preferably, they are not sugar-based. Preferred sweeteners include aspartame, acesulfame potassium (acesulfame K), sucralose and saccharine or combinations thereof. Alternatively, it can be preferred for compositions of the invention to be substantially free from added sweeteners, for example to minimize the number of different components in the compositions. When present, sweeteners may, for example, be present in an amount of 0.01 to 1 % w/w. More preferably, a sweetener may be present in an amount of 0.1 to 1% w/w. The level of sweetener required to obtain a satisfactory taste may depend on the presence, and identity and quantity, of the other components of the composition.

In general it is not necessary for a solid composition of the invention to include preservatives or anti-oxidants. Nevertheless, low levels of anti-oxidants or preservatives may be included if required. It is preferred that compositions of the present invention are also substantially free from "salt taste" masking agents, such as agents that mask the taste of sodium sulphate, (other than flavourings mentioned herein) and from salts of non-fatty acids such as salts of mineral acids.

A solid composition of the invention can be of any convenient size. As mentioned above, a tablet should be sufficiently large to provide the desired quantity of PEG to the subject, but not be so large as to be uncomfortable in the mouth, difficult to chew or suck, or difficult to package. A tablet may, for example, have a mass of 0.5 to 10g, more preferably 0.5 to 5g, for example 1.0 to 5.0g, for example 2.0 to 3.5g, for example 2.5 to 3.5g. In one embodiment, a tablet of the invention has a mass of from 2.5 to 3.0g, for example 2.75g. For certain uses, where a larger amount of PEG is to be delivered to the subject, a larger tablet may be convenient, for example having a mass of 3 to 10g, for example 3 to 5g, 3 to 7g, 4 to 7g, or 5 to 8g, for example 4 to 7g. For certain uses, where a smaller amount of PEG is to be delivered to the subject, for example for paediatric uses, a smaller tablet may be convenient, for example having a mass of 0.5 to 2.0g, for example 1.0 to 1.75g, for example 1.25 to 1.50g.

20

A solid composition of the invention for treating, ameliorating and/or preventing CRC may therefore be a solid composition of mass 2.0 to 3.5g comprising:

- (a) 1.00 – 3.15g polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
- (b) 0.20 – 1.40g of solid such as mannitol.

25

A solid composition of the invention for treating, ameliorating and/or preventing CRC may therefore be a solid composition of mass 2.5 to 3.5g comprising:

- (a) 1.25 – 3.15g polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
- (b) 0.25 – 1.40g of solid such as mannitol.

30

Similarly, a composition of the invention for treating, ameliorating and/or preventing CRC may therefore be a solid composition of mass 1.0 to 1.75g comprising:

- (a) 0.50 – 1.575g polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
- (b) 0.10 – 0.70g of solid such as mannitol.

As mentioned above, a lubricant (for example magnesium stearate) may be present in a solid composition of the invention in an amount of 2% w/w or less, for example 1% w/w or less. A solid composition of the invention of mass 2.0 to 3.5g may therefore comprise 0.07g or less of lubricant, for example 0.35g or less of lubricant. For example, it may comprise lubricant in an amount of 0.002 to 0.0315g, for example 0.004 to 0.028g, for example 0.006 to 0.0245g. A larger composition of the invention of mass 3.0 to 7.0g may comprise 0.14g or less of lubricant, for example 0.07g or less of lubricant. For example, it may comprise lubricant in an amount of 0.003 to 0.063g, for example 0.006 to 0.056g, for example 0.009 to 0.049g. A smaller composition of the invention of mass 1.0 to 1.75g may comprise 0.035g or less of lubricant, for example 0.0175g or less of lubricant. For example, it may comprise lubricant in an amount of 0.001 to 0.01575g, for example 0.002 to 0.014g, for example 0.003 to 0.01225g.

As mentioned above, flavouring may be present in a solid composition of the invention and, when present, it preferably makes up 0.1 to 15% w/w of the solid composition. A solid composition of the invention of mass 2.0 to 3.5g may therefore comprise 0.002 to 0.525g of flavouring, for example 0.002 to 0.175g, for example 0.002 to 0.07g, for example 0.004 to 0.07g of flavouring. A larger composition of the invention of mass 3.0 to 7.0g may comprise 0.003 to 1.05g of flavouring, for example 0.003 to 0.35g, for example 0.003 to 0.14g, for example 0.006 to 0.14g of flavouring. A smaller composition of the invention of mass 1.0 to 1.75g may comprise 0.001 to 0.2625g of flavouring, for example 0.001 to 0.0525g for example 0.001 to 0.021g, for example 0.002 to 0.021g of flavouring.

For example, a solid composition of the invention for treating, ameliorating and/or preventing CRC may comprise:

- (a) 50 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da;
- 5 (b) 10 – 30 % w/w of solid such as mannitol;
- (c) 0.1 – 2.0 % w/w lubricant; and
- (d) 0.1 – 15 % w/w flavouring.

10 In one embodiment, a solid composition of the invention for treating, ameliorating and/or preventing CRC comprises:

- (a) 70 – 90 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 3,000 to 8,000 Da;
- (b) 10 – 25 % w/w of solid such as mannitol;
- (c) 0.1 – 1.5 % w/w magnesium stearate; and
- 15 (d) 0.1 – 2.0 % w/w flavouring.

For example, a solid composition of the invention for treating, ameliorating and/or preventing CRC comprises:

- (a) 75 – 89 % w/w polyethylene glycol (PEG) having an average molecular weight within the range 3,000 to 4,000 Da;
- 20 (b) 10 – 20 % w/w of solid such as mannitol;
- (c) 0.2 – 0.8 % w/w magnesium stearate; and
- (d) 0.1 – 1.0 % w/w flavouring.

25 For example, a solid composition of the invention for treating, ameliorating and/or preventing CRC may comprise:

- (a) 1.00 – 3.15g polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da;
- (b) 0.20 – 1.40g of solid such as mannitol;
- 30 (c) 0.002 – 0.07g lubricant; and
- (d) 0.002 – 0.525g flavouring.

In one embodiment, a solid composition of the invention for treating, ameliorating and/or preventing CRC comprises:

- 5 (a) 1.40 – 3.15g polyethylene glycol (PEG) having an average molecular weight within the range 3,000 to 8,000 Da;
- (b) 0.20 – 0.875g of solid such as mannitol;
- (c) 0.002 – 0.0525g magnesium stearate; and
- (d) 0.002 – 0.07g flavouring.

10 For example, a solid composition of the invention for treating, ameliorating and/or preventing CRC comprises:

- (a) 1.5 – 3.115g polyethylene glycol (PEG) having an average molecular weight within the range 3,000 to 4,000 Da;
- (b) 0.20 – 0.70g of solid such as mannitol;
- 15 (c) 0.004 – 0.016g magnesium stearate; and
- (d) 0.002 – 0.035g flavouring.

For example, a solid composition of the invention for treating, ameliorating and/or preventing CRC comprises:

- 20 (a) 2273 to 2284mg polyethylene glycol (PEG) having an average molecular weight within the range 3,000 to 4,000 Da;
- (b) 420 to 446mg of solid such as mannitol;
- (c) 13.5 to 13.75mg magnesium stearate; and
- (d) 11 to 42mg of flavouring such as peppermint or raspberry/lemon
- 25 flavouring.

The solid compositions of the invention may be packaged in any convenient fashion. For example a plurality of units (e.g. tablets) of the solid composition of the present invention (such as 5, 10, 15 or 20) may be packaged in a way conventional in the vitamin

30 supplements industry. For example, they may be packed in a tube (such as a PTFE tube) equipped with a removable and replaceable closing means, for example a stopper.

Alternatively, the solid compositions of the invention may be provided in a jar or other container with a removable and replaceable lid, or in a bag or within a wrapper (for example a foil wrapper). A desiccant is preferably also present. Alternatively, they may be packaged in a blister pack. In an embodiment, the solid compositions are packaged
5 within a tube, jar, bag, wrapper or other container without any wrapping around individual units (e.g. tablets). Optionally, individual units of solid compositions of the present invention may have a wrapping. In a preferred embodiment, 30 units of the composition of the present inventions are provided spilt into three tubes (e.g. 10 units per tube) or other packaging optionally together with instructions for use. Units of the
10 present invention may also be provided in a refill bag enabling previously obtained tubes to be refilled with units of the invention.

The solid compositions of the invention can be taken on their own as presented and chewed or sucked by a subject. It is not necessary for a subject to take water or another
15 drink with the solid composition. Some subjects may wish to drink water or another fluid with or soon after taking a solid composition of the invention so as to facilitate the intake. The convenient packaging and the lack of a need to take water or another drink greatly increases the convenience of the solid compositions to subjects in comparison with other forms of PEG-based products currently on the market. Compositions of the present
20 invention may be consumed prior to eating a meal or snack, together with the meal or snack or following a meal or snack.

In one embodiment, the subject typically takes up to 6g (or thereabout) per day of PEG, for example 2 to 6g per day, for example 3 to 5g per day, for example 4 to 5g per day. In
25 that embodiment, the composition is free from components of a nature and quantity having a laxative effect. PEG is not considered to have significant laxative activity in an adult when taken at a level of 6g per day. Mannitol, flavouring and lubricant components are also not considered to have significant laxative activity at the daily levels at which they are provided when the composition provides up to 6g PEG per day. For a solid
30 composition of 2.0 to 3.5g total mass and comprising 85% PEG w/w, a healthy subject may be recommended to take 1 or 2, or 1, 2 or 3 per day (to provide up to 6g or

thereabout of PEG per day). For a smaller solid composition (of, for example, 1.0 to 1.75g total mass), a healthy subject may be recommended to take 1 to 6 per day, for example 2 to 5 per day (to provide up to 6g or thereabout of PEG per day). Conversely, for a larger solid composition (of, for example, total 3.0 to 7.0g total mass), a healthy
 5 subject may be recommended to take 1 or 2 per day (to provide up to 6g or thereabout of PEG per day).

Thus, the present invention provides a solid composition for oral administration as a solid (preferably having a mass of 1.0 to 5.0g) to a healthy subject (such as a human) for use in
 10 a method for treating, ameliorating and/or preventing CRC and optionally preventing constipation,

wherein the composition comprises:

- (a) 50 – 90 % w/w (for example 60 to 90% w/w, preferably 70 to 90% w/w, more preferably 70 to 89 % w/w, for example 75 to 89 % w/w, e.g. 78 to 89 %
 15 w/w, 80 to 85% w/w, 81 to 85 % w/w, 80 to 84 % w/w, 82 to 84 % w/w)
 polyethylene glycol (PEG) having an average molecular weight within the range 2,000 to 10,000 Da; and
- (b) 10 – 40 % w/w (for example 10 to 25% w/w, 10 to 20% w/w, preferably 12 to 20 % w/w, more preferably 12 to 19% w/w, 12 to 18% w/w, or 12 to 17 %
 20 w/w, e.g. 14 to 20% w/w, 14 to 19% w/w or 14 to 18% w/w 14 to 17% w/w) of a solid such as mannitol; together with
- (c) optional lubricant, optional flavouring and/or optional sweetener as described supra; and

wherein the method comprises administering said composition so that the subject
 25 consumes up to 6g (or thereabout) of PEG per day.

Preferably, said method comprises administering said composition so that the subject consumes between 2g and 6g, e.g. 2g to 5.5g per day. Preferably, said method is performed on a daily or alternate day basis. Preferably the method is performed over a
 30 period of at least two weeks, preferably at least a calendar month, more preferably at least

6 consecutive calendar months, or at least 12 consecutive calendar months, or at least 24 or at least 36 consecutive calendar months.

5 In certain embodiments of the invention described *supra*, the human subject may be one with a predisposition towards developing CRC based, e.g. on family history (e.g. family history of developing CRC), medical history (e.g. treatment of pre-existing colon polyps and/or the presence of a disease which predisposes an individual towards developing CRC e.g. familial polyposis or Lynch's syndrome and/or prior episode of CRC or colonic adenoma), health status or life style (for example due to high fat diet or heavy alcohol
10 intake).

Since the present inventors have determined that the mean age for diagnosis of CRC in the dataset analysis given below is 73.0 years for males and 74.9 years for females, compositions of the invention may be used to treat, ameliorate and/or prevent CRC in
15 humans aged 50 years or greater, e.g. 55 years or greater such as 60 years or greater, e.g. 60 to 70 years or 65 to 70 or 60 to 75 years.

In other embodiments, the human subject is not constipated and methods of the present invention may both prevent constipation and treat or prevent or ameliorate CRC in such
20 humans.

In other embodiments of the invention, a kit (e.g. package) comprising a plurality of units (for example 5 or more, 10 or more, 20 or more) of compositions of the invention as described *supra* together with directions for use are provided. For example, the
25 directions for use may state that one, two or three unit(s)/tablet(s) of the invention may be consumed per day either together or in a split dose (e.g. one tablet in the morning, one tablet in the evening). Accordingly therefore a composition in oral unit dosage form (e.g. tablet) for use in a method of treating, ameliorating and/or preventing CRC (and, optionally, preventing constipation) in humans comprises an amount (e.g. effective and
30 sub-laxative amount such as 2.2grams or thereabout) of a PEG and/or PEG block co-

polymer which method comprises administering one, two or three unit(s) of said composition per day. The composition may be used in a method such as described *supra*.

5 Compositions of the invention are therefore particularly beneficial for consumption by human subjects on a chronic (for example daily) basis since they have good mouthfeel and structural integrity and provide an amount of PEG useful in the context of colorectal cancer (particularly in conjunction with the methods of the invention) yet avoids the excessive gastrointestinal disturbances (such as loose stools) that may be regarded as unpleasant or generally unacceptable when consuming larger amounts of PEG on such a
10 chronic basis.

It will be understood by the reader of this specification, that all embodiments described *supra* may be construed as to disclose, separately, an embodiment directed to PEG and an embodiment directed to PEG block co-polymer.

15 It will be apparent to the reader of this specification, that the term “comprising” and grammatical variations thereof, in relation to embodiments of the invention described *supra*, may instead be “consisting essentially of” or “consisting of”.

20 The following examples illustrate but do not limit the invention.

Example 1: Study of association between exposure to a macrogol laxative and the risk of colorectal cancer

25 **1. Study objectives**

- To describe the incidence of colorectal cancer on the General Practice Research Database (GPRD) following different types of laxative exposure.
- To evaluate any association between exposure to a macrogol laxative and the risk of colorectal cancer.

30

2. Methods

Data source and study population

The GPRD

- The General Practice Research Database (GPRD) is a computerised database containing anonymised longitudinal data collected within UK primary care. It consists largely of
- 5 coded data entered onto a computer system by general practitioners (GPs) as part of the clinical management of patients within primary care. Information entered onto the system includes demographic details, symptoms and medical diagnoses, detailed prescription data, hospital referrals and admissions and the results of clinical investigations and tests.
- 10 The longitudinal nature of the data combined with large sample sizes and high quality data on consultations, risk factors, diagnoses, prescribing and outcomes means the GPRD has a number of advantages for research. The age and sex distribution of the patient population in the database at any point in time closely matches the Office for National
- 15 Statistics estimates for the total England and Wales population. In addition, for many co-morbidities, GPRD figures correlate well with those for other UK sources such as cancer statistics and figures reported by the Office for National Statistics. The GPRD is a widely used and validated source of epidemiological data and is a valuable resource for epidemiological research.

20 Study design considerations

- The nature of both the exposure and the outcome of interest for this study meant that the following considerations needed to be taken into account when deciding on the most appropriate study design:
1. Laxative users will differ in terms of their risk of CRC from non-laxative users.
 - 25 Therefore, to diminish the risk of 'confounding by indication' any association will need to be evaluated within the population of laxative users;
 2. The risk of CRC increases exponentially with age. Therefore it is important that any matching between cases and controls is carried out based on the patients' year of birth and not on wider age bands;
 - 30 3. CRC has a long latency period and exposure status at the time of diagnosis

(classically the way exposure status is measured in epidemiological studies) will not be the relevant exposure status;

4. Changes in bowel movements might be the first presenting symptoms of CRC and therefore care needs to be taken when evaluating any association between laxative use and CRC that the laxatives were not prescribed because of the first presenting symptoms of CRC;

5. Laxative use is often on an 'as needed' basis, is intermittent, and people switch between products.

Given the complexities of the association of interest it was concluded that no single study design could provide the complete answer. In order to create a full picture of investigations, it was decided that it would be necessary to carry out a study of CRC incidence rates in different laxative exposure groups combined with a case-control study nested within the cohort study population.

The methods and results of both of these studies will now be discussed in turn.

A. Descriptive studies of laxative use and CRC incidence

Study period

Movicol[®] was licensed for use in the UK in 1998 and the study period ran from 1 January 2000 until 31 March 2009. Secular trends in prescribing data presented in this report, however, are given from January 1992 until December 2008: the last full calendar year for which data was available.

Study population

The study population consisted of all patients on the GPRD permanently registered at, or transferred out of, a GP practice providing data that the MHRA considered to be up-to-standard for the purposes of research and who had received ≥ 1 laxative prescription during the time period their medical record was considered to be UTS (up-to-standard). There were no age restrictions.

Identification of patients with colorectal cancer

Colorectal cancer was defined according to the International Classification of

Diseases 9th edition and included ICD-9 153-154.1 (inclusive). The GPRD coding system, however, does not use ICD codes, so incident cases of colorectal cancer were identified on the GPRD using a combination of “read codes” and the application of three different algorithms.

5

Identification of laxative users

Patients were eligible for inclusion in the cohort study from the day after their first recorded laxative prescription onwards. Laxative products were taken as those classified under chapter 1.6.1 – 1.6.5 of the British National Formulary (BNF). PEG based products at chapter 1.6.4 of the BNF include MOVICOL[®] which contains approximately 13.125g of macrogol 3350.

10

Patients were not included if their only laxative prescription(s) were recorded outside of the time period that their medical record was considered to be up-to-standard (UTS).

15 Classification of laxative exposure

The laxative exposure of patients was classified into three categories

- i. Non-macrogol user only
- ii. Macrogol user only or before other laxative use
- iii. Macrogol user after other laxative use

20

Up to the point someone received their first macrogol prescription on the GPRD, they were classified as ‘non-macrogol user only’. From the point of receiving a prescription for a macrogol they were classified as either ‘macrogol user only or before other’ or ‘macrogol user after other’, as appropriate. This was done because, at the time of study, the following uncertainties existed: a) laxatives other than macrogols were not thought to cause any in- or decrease in CRC risk; b) it was unclear whether one dose of macrogol could have an impact on CRC risk, whether there was a threshold effect (a minimum number of dosages was needed to achieve a reduction in CRC risk) or whether there was a dose or duration-response association; and c) whether, if there was a reduction in CRC risk caused by macrogol utilisation, this was because of a reduction in tumour initiation or a reduction in tumour progression.

30

B. Case-control study

Study population

- 5 The case-control study was nested within the cohort of laxative users so all cases and controls were recruited from the laxative user cohort identified supra. Cases and controls were eligible for study inclusion after the date of their first laxative prescription.

10 Classification of laxative exposure

As with the cohort study, laxative exposure of patients was classified into three categories

- i. Non-macrogol use only
- ii. Macrogol use only or before other laxative use ('macrogol first')
- iii. Macrogol use after other laxative use ('other laxative first')

- 15 Over the course of most of the study period, categories i. and iii. would have reflected common practice in accordance with prescribing guidelines, whereas category ii would have been unusual. This changed in 2006 and it is anticipated to change further following the recent publication of a Cochrane review that concludes macrogols are the laxative of first choice.

20

Identification of colorectal cancer cases

Colorectal cancer cases were all patients with CRC newly diagnosed between 1 January 2000 and 31 March 2009 and they were identified using the algorithms and methods described for the cohort study supra. The index date was taken as the earliest date with

- 25 evidence of a CRC diagnosis and was determined using the same criteria as for the descriptive study of CRC incidence rates. Colorectal cancer cases were required to have ≥ 6 months of UTS data before the CRC index date to enable information on covariates to be collected.

30 Identification of controls

Six controls were identified for each CRC case in order to achieve optimum statistical power. By definition, controls have to be sampled from the population that gave rise to the cases. Therefore, controls were sampled from the same laxative cohort population and they were required to be disease free (have no diagnosis of colorectal cancer) on and before the index date of the case. In addition, to eliminate confounding by age and sex, they had to have the same year of birth and be of the same sex as the case. Controls were also required to have ≥ 6 months of UTS data before the index date of the case to enable information on covariates to be collected and they were required to have received ≥ 1 prescription for a laxative before the CRC index date of the matched case.

Power considerations

Based on the assumption macrogols had 10% of the laxative market share and with the selection of 6 controls per case, to demonstrate a 20% reduction in CRC risk the nested case-control study of CRC risk required approximately 2,360 newly diagnosed cases; to demonstrate a 25% reduction in risk 1,480 cases was required. If macrogols had 20% of the market then these numbers became 1,290 and 800 respectively.

Back dating of the colorectal cancer index date

As exposure on the index date was unlikely to be relevant additional sets of controls were selected on the index date minus 6 months, minus 12 months, minus 18, 24, 30, 36, 42, 48, 54 and 60 months and for each of these analysis sets the analyses of exposure and risk factors were carried out based on the 'new' index dates. This means that any changes in exposure status or risk factors during the period between the 'new' index date and the original index date were ignored on the basis that these were irrelevant because the cancer was already present but had simply not been diagnosed yet.

It was hypothesised that if macrogol laxatives did decrease CRC risk then any association found should become stronger or remain stable with back dating of the index date.

Dose response relationship

For the osmotic laxatives, the total dosage received (millilitres of lactulose and sachets of macrogols) was calculated for all cases and controls. The association between CRC risk and laxative dosage prescribed was evaluated.

5 Identification of data on potential risk factors for colorectal cancer

Information was collected, where available, for both cases and controls for each of the covariates listed below. CRC risk is related to diet and information on diet is not recorded within the GPRD. However, information on socioeconomic status (SES) and body mass index (BMI) was included as proxy measures.

10

Covariates present on the GPRD and reported or suggested to either be risk factors for, or have a protective effect against, colorectal cancer.

Covariates

15

Smoking

Alcohol

Body mass index (BMI)

Socioeconomic status (SES)

Inflammatory bowel disease (IBD)

20

Cancer diagnosis other than colorectal cancer

Diabetes

Cholecystectomy

Prescriptions for:

Low dose aspirin (<300mg)

25

Non-low dose aspirin (≥ 300 mg)

COX-2 inhibitors

Non-aspirin non-selective NSAIDs

Dantron containing laxatives

Statins

30

Opioids

Hormone replacement therapy (HRT)

Calcium supplements

5-ASA

5 Statistical analyses

Conditional logistic regression analyses were carried out to evaluate any association between macrogol exposure and colorectal cancer risk. All covariates significant at the level of $p < 0.20$ in the univariate analyses were considered for inclusion in the multivariate models. Covariates remained in the multivariate model if $p \leq 0.05$ or if they altered the risk estimate by more than 10%. Tests were carried out for interactions between variables and the stability of the models was assessed using the Hosmer-Lemeshow statistic.

C. Results

15 Incidence of colorectal cancer on the GPRD.

A total of 14,598 potential incident CRC cases were identified on the GPRD between 1 January 2000 and 31 March 2009, in addition to which there were 255 cases of cancer of the anus that were included for the comparison of CRC incidence on the GPRD with UK figures reported by the cancer registries. Of the total 14,853 colorectal and anus cancer cases identified, 2,402 (16.7%) had a code specifically stating the type of cancer but with no record of supporting evidence for the diagnosis.

Laxative drug utilisation on the GPRD

We identified 872,959 patients on the GPRD who had received a total of 9,866,699 laxative prescriptions between 1 January 1992 and 31 March 2009. A total of 721,513 macrogol laxative prescriptions were identified for 155,609 individuals, of which 1,297 (0.2%) were prescriptions for bowel cleansing preparations (Klean-Prep® or Moviprep®).

30 The annual number of laxative prescriptions recorded on the GPRD was found to increase over time in line with the increase in the number of patients contributing data to the

database. In 2007 a total of 836,391 prescriptions were issued for laxative products. The reason for a slight reduction in the number of prescriptions recorded in 2008 is likely to be the result of the delay in some GP practices uploading their latest data collection to the MHRA. A continuous steady increase was observed in the number of prescriptions for
 5 macrogol laxatives following the first marketing authorisation of Movicol®.

Approximately two-thirds of laxative prescriptions on the GPRD were prescribed to females and one-third to males. A slightly larger proportion of macrogol prescriptions were issued to children and adolescents and to adults aged between 30 and 59 compared
 10 with all types of laxative prescriptions.

Case-control study

We identified 4,734 eligible incident cases of colorectal cancer. Of the 4,734 CRC cases, 1,592 (33.6%) had only received a prescription for a laxative in the 6 months before the
 15 CRC index date.

Of these cases, 49.3% were male and 50.7% were female. CRC is more common in males but the slightly larger proportion of female cases identified is likely to reflect the age and sex distribution of the laxative user cohort combined with the fact that on average, women live longer than men. The mean age at diagnosis was 73.0 years (SD =
 20 10.9) and 74.9 years (SD = 12.2) for males and females respectively.

These cases were therefore only eligible to be included in the index date analysis set – Table 1.

Table 1: Number of cases and matched controls in each of the backdated analysis sets

Analysis set	Cases (n)	Controls (n)
Index date	4,734	28,404
Index date -6m	3,142	18,852
Index date -12m	2,722	16,332
Index date -18m	2,445	14,670
Index date -24m	2,195	13,170
Index date -30m	1,982	11,892

Index date -36m	1,789	10,734
Index date -42m	1,636	9,816
Index date -48m	1,481	8,886
Index date -54m	1,351	8,106
Index date -60m	1,214	7,284

A potential dose–response relationship was observed for cohort in the “macrogol exposure following other” at 24 months (Table 2) and 36 months (Table 3) before the index date.

Table 2 - Total Macrogol exposure 24 months before the index date.

No: of sachets	N	(Cases)	Odds Ratio	95% CI
<20	99	(14)	1.02	0.57-1.80
21-30	124	(17)	0.98	0.58-1.66
31-60	154	(22)	0.97	0.62-1.54
61-180	144	(13)	0.57	0.32-1.02
>180	140	(11)	0.50	0.27-0.94

Table 3 - Total Macrogol exposure 36 months before the index date

No. of sachets	N	(cases)	Odds Ratio	95% CI
<20	76	(7)	0.61	0.28-1.34
21-30	70	(8)	0.75	0.36-1.59
31-60	94	(11)	0.80	0.42-1.52
61-180	85	(5)	0.36	0.15-0.90
>180	82	(6)	0.45	0.20-1.04

10

Since Movicol® contains approximately 13.125g of macrogol 3350 per sachet, a calculation can be made as to total macrogol exposure over the respective time frames that demonstrate a reduction in risk of CRC. See Tables 4 and 5 below wherein the total

macrogol exposure over 24 months and 36 months respectively, together with 12 month, one month, one week and one day equivalent is provided.

5 Table 4: 24 month Macrogol exposure (grams).

No: of sachets	24 month	12 month equivalent	One month equivalent	One week equivalent	One day equivalent
61-180	800.6-2362.5	400.3-1181.3	33.3-98.4	7.7-22.7	1.1-3.2
180+	2362.5+	1181.3+	98.4+	22.7+	3.2+

Table 5: 36 month Macrogol exposure (grams)

No: of sachets	36 month	12 month equivalent	One month equivalent	One week equivalent	One day equivalent
61-180	800.6-2362.5	266.9-787.5	22.2-65.6	5.1-15.1	0.73-2.2
180+	2362.5+	787.5+	65.6+	15.1+	2.2+

Example 2: Tablets containing different w/w % of mannitol, useful in the invention

The tablets described in Table 6 were prepared by combining the dry ingredients and compressing in a punch and die machine. For tablets 2A to 2C, the machine was a
 5 Manesty 16 punch D machine with a standard stainless steel punch and die with flat 22mm diameter and beveled edge with PTFE and vulcalon inserts from I Holland Ltd. For tablets 2D and 2E, the unit formula amounts were compressed on a Manesty D machine at normal manufacturing speed and with a standard stainless steel punch and die with flat 22mm diameter and beveled edge. The properties of the tablets were noted and
 10 they are given in Table 6b below.

Tablet 2A had an acceptable taste. However, the tablets were prone to sticking to the tableting machine, and many tablets were capped or laminated, making them unusable. Tablet 2B contained the same flavouring as tablet 2A, but more mannitol (15.3% vs.
 15 9.1% in 2A) and less flavouring (1.5% vs. 5.4%). Tablet 2B had an acceptable taste and there was no evidence of sticking to the tableting machine, or capping or laminating of the tablets. Tablet 2C contains similar amounts of PEG, mannitol and magnesium stearate to tablet 2B, but the flavouring is peppermint. It displays similar characteristics to tablet 2B. Tablet 2D contained no flavouring, and 10% mannitol. It displayed no
 20 capping or sticking and only a small amount of chipping. Tablet 2E contained no flavouring, and 40% mannitol. It displayed good manufacturing characteristics. Tablets 2D and 2E had a bland taste as compared with tables 2A to 2C. This is most likely because of the absence of flavouring. The taste was, however, not unpleasant. Tablets 2F to 2H all displayed good manufacturing characteristics and an acceptable taste.

25

It is seen that a tablet containing from 59.5 to 89.5% w/w PEG (in particular 82.7 or 82.9% w/w PEG) and 10 to 40% /w mannitol (in particular 15.3 or 16.2% w/w mannitol) has better ease of manufacture characteristics than a tablet containing 85.0% PEG and 9.1% mannitol.

Table 6a – Composition of Tablets 2A to 2E

Component	Tablet 2A		Tablet 2B			Tablet 2C			Tablet 2D		Tablet 2E	
	Unit formula	5kg bag blend	Unit formula	5kg bag blend	255kg batch	Unit formula	5kg bag blend	255kg batch	Unit formula	5kg bag blend	Unit formula	5kg bag blend
PEG av. MW 3000-4000	2339mg (85.0%)	4.25kg	2273.7mg (82.7%)	4.144kg	211kg	2284mg (82.9%)	4.155kg	212kg	2685mg (89.5%)	4.48kg	1785mg (59.5%)	2.98kg
Mannitol	250mg (9.1%)	0.45kg	420.75 mg (15.3%)	0.765kg	39kg	446mg (16.2%)	0.810kg	41kg	300mg (10%)	0.50kg	1200mg (40%)	0.75kg
Magnesium Stearate	13.75mg (0.5%)	0.03kg	13.75mg (0.5%)	0.025kg	1kg	13.75mg (0.5%)	0.025kg	1kg	15mg (0.5%)	0.03kg	15mg (0.5%)	0.03kg
Flavouring	150mg (5.4%) (raspberry- lemon)	0.27kg	41.8mg (1.5%) (raspberry- lemon)	0.075kg	4kg	11mg (0.4%) (pepper mint)	0.020kg	1kg	-	-	-	-
Total wt	2752.75 mg		2749.3 mg			2754.75 mg			3000mg		3000mg	

Table 6a (cont)

Component	Tablet 2F		Tablet 2G		Tablet 2H	
	Unit formula	5kg bag blend	Unit formula	5kg bag blend	Unit formula	5kg bag blend
PEG av. MW 3000-4000	2270mg (79%)	3.96Kg	2045mg (74%)	3.705Kg	1900mg (69%)	3.46Kg
Mannitol	574mg (20%)	1.0Kg	690mg (25%)	1.25Kg	827mg (30%)	1.5Kg
Magnesium Stearate	14mg (0.49%)	0.025Kg	14mg (0.5%)	0.025Kg	14mg (0.5%)	0.025Kg
Flavouring	11mg (Peppermint) (0.38%)	0.02Kg	11mg (peppermint) (0.4%)	0.02Kg	11mg (Peppermint) (0.4%)	0.02Kg
Total wt	2870mg	5.0Kg	2760mg	5.0Kg	2756mg	5.0Kg

Table 6b – Properties of Tablets 2A to 2E

Ease of Manufacture	Some capping, chipping and sticking to punches	Reliable manufacture with minimal capping, chipping or sticking at 255kg scale. Good weights and hardness throughout batch at 5kg scale.	Reliable manufacture with minimal capping, chipping or sticking at 255kg scale. No sticking or capping; good weight and hardness control; good appearance at 5kg scale.	Some chipping of tablets, but acceptable. Weight and hardness consistent	Good control, good appearance
Taste	Acceptable taste	Acceptable taste	Acceptable taste	Bland	Bland
Hardness	Not measured	8.95-14.29kg (measured for 5kg batch)	6.34-9.19kg (measured for 5kg batch)	4.42-7.34kg	5.96-10.2kg

Table 6b (cont) – Properties of Tablets 2F to 2H

Ease of Manufacture	Appearance of tablet good, no capping	Appearance of tablet good, no capping	Appearance of tablet good, no capping
Taste	Acceptable taste	Acceptable taste	Acceptable taste
Hardness	6.28-14.4Kg	5.12-7.5Kg	7.27Kg – 10.15Kg

Example 3: Comparison of tablets containing mannitol and different w/w % of magnesium stearate, useful in the invention

- The tablets described in Table 7a were prepared. The materials were dispensed and then
- 5 bag blended. The unit formula amounts were compressed on a Manesty D machine at normal manufacturing speed and with a standard stainless steel punch and die with flat 22mm diameter and beveled edge and PTFE inserts. The properties of the tablets were noted and they are given in Table 7b below.
- 10 It is seen in Tables 7a and 7b that tablets containing PEG and 15% w/w mannitol and 0.2%, 0.5% or 5.0% w/w magnesium stearate have good manufacturing properties and acceptable taste.

Table 7a – Composition of Tablets 3A to 3C

Component	Tablet 3A		Tablet 3B		Tablet 3C	
	Unit formula	5kg bag blend	Unit formula	5kg bag blend	Unit formula	5kg bag blend
PEG average MW 3000-4000	2544mg (84.8%)	4.24kg	2400mg (80%)	4.0kg	2535mg (84.5%)	4.23kg
Mannitol	450mg (15%)	0.75kg	450 mg (15%)	0.75kg	450mg (15%)	0.75kg
Magnesium Stearate	6mg (0.2%)	0.01kg	150mg (5%)	0.25kg	15mg (0.5%)	0.03kg
Flavouring	-	-	-	-	-	-
Total wt	3000 mg		3000 mg		3000 mg	

Table 7b – Properties of Tablets 3A to 3C

Ease of Manufacture	Tablets good, no capping	Tablets good	Slight capping
Taste	Bland taste	Bland taste, slightly artificial	Better taste
Hardness	5.4-11.0kg	4.42-7.34kg	0.4-6.1kg

Example 4: Comparison of various flavours of PEG+mannitol tablets, useful in the invention

- Tablets analogous to the tablets of Example 2 with a variety of flavourings were prepared by combining the dry ingredients and compressing in a punch and die machine. The machine was a Manesty 16 punch D machine with a standard stainless steel punch and die with flat 22mm diameter and beveled edge with PTFE and vulcalon inserts from I Holland Ltd.
- The tablets were provided to a panel of tasters. They were asked to taste each of the tablets and score them with an emphasis on the flavour, scoring from 1 (unpleasant) to 5 (pleasant). There were 22 tasters and their scores were summed together. It was found that peppermint flavoured tablets (score = 65) and lemon-raspberry flavoured tablets (score = 87) were preferred over lemon-lime flavoured tablets (score = 37) and orange flavoured tablets (score = 23).

Example 5: Comparison of Tablets containing various other solids, useful in the invention.

- Tablets containing solids other than mannitol were prepared in the same manner as the tablets of Example 2 *supra*. The composition and properties of these tablets are noted in Table 8a and 8b below.

Table 8a – Comparison of Alternative Solids

Component	Tablet 5A Unit amount/ 5Kg blend	Tablet 5B Unit amount/ 5Kg blend	Tablet 5C Unit amount/ 5Kg blend
PEG av. MW 3000-4000	2276mg/4.145Kg (83%)	2279mg/4.145Kg (83%)	2280mg/4.145Kg
Solid	<u>Sorbitol</u> 445mg/0.81Kg (16.2%)	<u>Lactose/Starch[†]</u> 446mg/0.81Kg (16.2%)	<u>Xylitol</u> 446mg/0.81Kg

Magnesium Stearate	14mg/0.025Kg (0.51%)	14mg/0.025Kg (0.51%)	14mg/0.025Kg (0.51%)
Flavouring	11mg/0.02Kg (0.40%)	11mg/0.02Kg (0.40%)	11mg/0.02Kg (0.40%)
Total wt	2746mg / 5.0Kg	2753mg/5.0Kg	2750mg/5.0Kg

1. Lactose / starch compound, StarLac® (Roquette Pharma, Northants, UK) is a spray-dried compound consisting of 85% alpha-lactose monohydrate (Ph. Eur. /USP-NF) and 15% maize starch (Ph. Eur. /USP-NF) dry matter.

5

Table 8b – Properties of Tablets 5A to 5C

Ease of Manufacture	Tablet appearance good, no capping	Tablet appearance good, no capping	Tablet appearance good, no capping
Taste	Tasted ok but lacked enhanced mouthfeel of mannitol tablets	Good hardness, tasted bland	Tasted ok, but tablet too soft
Hardness	6.97-10.09Kg	4.13-9.4Kg	4.67-7.99Kg

10 **Example 6 - Comparison of Tablets containing further various solids, useful in the invention**

Tablets containing solids other than mannitol were prepared in the same manner as the tablets of example 2 *supra*. The composition and properties of these tablets are noted
15 in Table 9a and 9b below.

Table 9a – Comparison of alternative solids

Component	Tablet 6A Unit amount/5Kg blend	Tablet 6B Unit amount/5Kg blend	Tablet 6C Unit amount/5Kg blend
PEG av. MW 3000-4000	2279mg/4.145Kg (82.9%)	2279mg/4.145Kg (82.9%)	2263mg/4.145Kg (82.9%)

Solid	<u>Lactose</u> 445mg/0.810Kg (16.2%)	<u>Dextrate</u> ¹ 440mg/0.800Kg (16.0%)	<u>Cellulose</u> ² 442mg/0.810Kg (16.2%)
Magnesium Stearate	14mg/0.025Kg (0.5%)	14mg/0.025Kg (0.50%)	13.6mg/0.025Kg (0.5%)
Flavouring	11mg/0.020Kg (0.4%)	11mg/0.020Kg (0.4%)	11mg/0.020Kg (0.4%)
Total wt	2750mg/5.0Kg	2746mg/4.99Kg	2730mg/5.0Kg

¹ Emdex[®], available from JRS Pharma, Rosenberg, Germany.

² Avicel[®], microcrystalline cellulose, available from FMC biopolymers, Philadelphia, USA.

5 **Table 9b – Properties of Tablets 6A to 6C**

Ease of Manufacture	Tablet appearance good, no capping, hardness good	Tablet appearance good, some capping	Tablet appearance good, no capping
Taste	Taste ok, but very bland	Pleasant taste but quite soft	Taste unpleasant
Hardness	5.2-13.6Kg	5.4-11.9Kg	7.1-13.4Kg

Conclusies

1. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, welke werkwijze het toedienen van ongeveer 800 gram of meer (zoals tussen 800 gram en 2365 gram) PEG of PEG blokcopolymeer gedurende een periode van 36 achtereenvolgende kalendermaanden omvat.
2. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, welke werkwijze het toedienen van ongeveer 800 gram of meer (zoals tussen 800 gram en 2365 gram) PEG of PEG blokcopolymeer gedurende een periode van 24 achtereenvolgende kalendermaanden omvat.
3. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, welke werkwijze het toedienen van ongeveer 800 gram of meer (zoals tussen 800 gram en 2365 gram) PEG of PEG blokcopolymeer gedurende een periode van 18-36 achtereenvolgende kalendermaanden omvat.
4. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, welke werkwijze het toedienen van tussen 0.1 gram en 6.0 gram PEG of PEG blokcopolymeer op een dagelijkse basis omvat.
5. Samenstelling volgens één van de voorgaande conclusies voor het behandelen van CRC in mensen.
6. Samenstelling volgens één van de conclusies 1-4 voor het beter maken van CRC in mensen (door bijvoorbeeld de verbreiding en/of groei van afwijkende crypt foci (ACF) te reduceren).
7. Samenstelling volgens één van de conclusies 1-4 voor het voorkomen van CRC in mensen.

8. Samenstelling volgens één van de voorgaande conclusies voor het behandelen, beter maken en/of voorkomen van CRC in mensen en voor het gelijktijdig gebruik bij het voorkomen van constipatie en/of het handhaven van de normale maag-darm-doorgangstijd in mensen.
- 5 9. Samenstelling volgens één van de voorgaande conclusies, waarin de werkwijze het toedienen van tussen 266 en 1181 gram (bijvoorbeeld tussen 400.3 en 1181.3 gram of tussen 266.9 en 787.5 gram of 400.3 en 787.5 gram) PEG of PEG blokcopolymeer gedurende een periode van 12 achtereenvolgende kalendermaanden omvat.
- 10 10. Samenstelling volgens één van de voorgaande conclusies, waarin de werkwijze het toedienen van tussen 22 en 98 gram (bijvoorbeeld tussen 33.3 en 98.4 gram of tussen 22.2 en 65.6 gram of 65.6 gram en 98.4 gram) PEG of PEG blokcopolymeer gedurende een periode van één maand omvat.
- 15 11. Samenstelling volgens één van de voorgaande conclusies, waarin de werkwijze het toedienen van tussen 5.1 en 22.7 gram (bijvoorbeeld tussen 7.7 en 22.7 gram of tussen 5.1 en 15.1 gram of tussen 15.1 en 22.7 gram) PEG of PEG blokcopolymeer gedurende een periode van één week omvat.
- 20 12. Samenstelling volgens één van de voorgaande conclusies, waarin de werkwijze het toedienen van tussen 0.73 en 3.22 gram (bijvoorbeeld tussen 1.1 en 3.2 gram of tussen 0.73 en 2.2 gram; of 2.2 en 3.2 gram) PEG of PEG blockcopolymeer gedurende een periode van één dag omvat.
- 25 13. Samenstelling volgens één van de voorgaande conclusies, welke tussen 0.2 en 6.4 gram PEG of PEG blokcopolymer omvat.
14. Samenstelling volgens één van de voorgaande conclusies, welke tussen 3.0 en 5.0
- 30 gram PEG of PEG blokcopolymer omvat.
15. Samenstelling volgens één van de voorgaande conclusies, welke tussen 1.0 en 4.0 gram PEG of PEG blokcopolymer omvat.

16. Samenstelling volgens conclusie 15, welke tussen 1.5 en 2.5 gram PEG of PEG
blokcopolymer omvat.
17. Samenstelling volgens conclusie 16, welke tussen 2.0 en 2.5 gram PEG of PEG
5 blokcopolymer omvat.
18. Samenstelling volgens conclusie 17, welke 2.2 gram, of een waarde daaromtrent,
PEG of PEG blokcopolymer omvat.
- 10 19. Samenstelling volgens één van de conclusies 13-18, welke dagelijks gedurende een
periode van 24 of 36 achtereenvolgende kalendermaanden wordt toegediend.
20. Samenstelling volgens één van de conclusies 13-18, welke met tussenpozen
gedurende een periode van 24 of 36 achtereenvolgende kalendermaanden wordt
15 toegediend.
21. Samenstelling volgens één van de voorgaande conclusies, waarin het PEG een
gemiddeld molecuulgewicht in het gebied van 1000 -8000 Dalton heeft.
- 20 22. Samenstelling volgens conclusie 21, waarin het PEG een gemiddeld
molecuulgewicht in het gebied van 3000 8000 Dalton heeft.
23. Samenstelling volgens conclusie 22, waarin het PEG een gemiddeld
molecuulgewicht heeft geselecteerd uit de groep bestaande uit; 3350, 4000, 6000,
25 8000 Dalton.
24. Samenstelling volgens conclusie 23, waarin het PEG geselecteerd wordt uit de
groep bestaande uit macrogol 3350, macrogol 4000, macrogol 6000, macrogol
8000.
30
25. Samenstelling volgens één van de voorgaande conclusies, waarin het mens aanleg
heeft voor het ontwikkelen van CRC (toe te schrijven aan bijvoorbeeld erfelijke
voorgeschiedenis en/of medische voorgeschiedenis zoals een eerder voorval van

CRC of darmpoliepen, Lynch syndroom, overerfbare polyposis en/of gezondheidssituatie en/of levensstijl).

26. Samenstelling volgens één van de voorgaande conclusies, waarin het mens 50 jaar of ouder is, bijvoorbeeld 55 jaar of ouder, zoals 60 jaar of ouder, bijvoorbeeld 60-75 jaar of 65-75 jaar.
27. Samenstelling volgens één van de voorgaande conclusies in de vorm van een orale dosis.
28. Samenstelling volgens één van de voorgaande conclusies, welke samenstelling de vorm heeft van een tablet, capsule, capsulevormige tablet, pil, poeder, granules, vloeistof.
29. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, welke samenstelling omvat:
 - (a) 50-90 gew% polyethyleenglycol (PEG) met een gemiddeld molecuulgewicht in het gebied van 2000-10000 Da; en
 - (b) 10-40 gew% van een vaste stof;
 - (c) optioneel verdere hulpstoffen zoals smaakstoffen, zoetstoffen en smeermiddelen.
30. Samenstelling volgens conclusie 29, welke is een vaste-stof samenstelling voor orale toediening als vaste stof.
31. Samenstelling volgens conclusie 29 of 30, welke samenstelling de vorm van een tablet heeft (zoals kauw- of zuigtabletten).
32. Samenstelling volgens één van de conclusies 29-31, waarin de vaste-stof component (b) geselecteerd wordt uit de groep bestaande uit; sorbitol, lactose, lactose en zetmeel (bijvoorbeeld een verbinding die lactosemonohydraat en maïszetmeel zoals Starlac® omvat), dextraten, cellulose, xylitol, maltitol en mannitol.

33. Samenstelling volgens één van de conclusies 29-32, welke 82-84 gew% PEG omvat.
34. Samenstelling volgens één van de conclusies 29-33, welke 10-20 gew% vaste-stof component (b) omvat.
35. Samenstelling volgens conclusie 34, waarin de vaste stof van component (b) bestaat uit mannitol, bijvoorbeeld mannitolgranules.
36. Samenstelling volgens één van de conclusies 29-35, waarin het PEG een gemiddeld molecuulgewicht in het gebied van 3000-4000 Da heeft.
37. Samenstelling volgens één van de conclusies 29-36, welke omvat:
- (a) 70-90 gew% polyethyleenglycol (PEG) met een gemiddeld molecuulgewicht in het gebied van 2000-10000 Da;
 - (b) 10-20 gew% van een vaste stof zoals mannitol;
 - (c) 0-2.0 gew% smeermiddel; en
 - (d) 0-2.0 gew% smaakstof.
38. Samenstelling volgens conclusie 37, welke PEG en mannitol in een gewichtsratio PEG: mannitol van 3:1-9:1 omvat.
39. Samenstelling volgens één van de conclusies 29-38, welke een smeermiddel in een hoeveelheid van 2.0 gew% of minder omvat, bijvoorbeeld 0.2-0.8 gew%, bijvoorbeeld 0.5 gew%.
40. Samenstelling volgens conclusie 39, waarin het smeermiddel magnesiumstearaat is.
41. Samenstelling volgens één van de conclusies 29-40, welke een smaakstof omvat.
42. Samenstelling volgens conclusie 41, waarin de smaakstof pepermunt is, bij voorkeur aanwezig in een hoeveelheid van 0.1-1 gew% (bijvoorbeeld 0.4 gew%),

of framboos-citroen, bij voorkeur aanwezig in een hoeveelheid van 0.5-2 gew% (bijvoorbeeld 1.5 gew%).

43. Samenstelling volgens één van de conclusies 29-42, welke is in wezen vrij van elektrolyten (bijvoorbeeld natriumchloride, kaliumchloride, bicarbonaten zoals natriumbicarbonaat, sulfaten zoals natriumsulfaat of fosfaten).
44. Samenstelling volgens één van de conclusies 29-43, welke een massa van 0.5-10 g heeft, bijvoorbeeld 1.0-5.0 g.
45. Samenstelling volgens één van de conclusies 29-44, welke een massa van 2.0-3.5 g heeft, en omvat:
 - (a) 1.00-3.15 g polyethyleenglycol (PEG) met een gemiddeld molecuulgewicht in het gebied van 2000-10000;
 - (b) 0.20-1.40 g mannitol.
46. Samenstelling volgens conclusie 29, welke in hoofdzaak is als hierin beschreven met verwijzing naar één van de voorbeelden 2-6.
47. Samenstelling volgens één van de conclusies 29-46 voor gebruik in een werkwijze volgens één van de conclusies 1-28.
48. Kit of parts welke een veelheid van doses van de samenstelling volgens één van de conclusies 29-47 omvat, samen met gebruiksaanwijzingen.
49. Samenstelling of werkwijze volgens één van de voorgaande conclusies, waarin de samenstelling of werkwijze een PEG blokcopolymeer zoals Pluronic ® F68 omvat.
50. Samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van CRC in mensen, waarin de werkwijze het toedienen van tussen 0.2 en 6.4 gram PEG of PEG blokcopolymeer op een dagelijkse basis omvat, waarin ongeveer 800 gram of meer PEG of PEG blokcopolymeer wordt toegediend gedurende een periode van 24 of 36 achtereenvolgende kalendermaanden.

51. Samenstelling volgens conclusie 50, welke tussen 1.0 en 4.0 gram PEG of PEG
blokcopolymer omvat.

52. Samenstelling volgens conclusie 51, welke tussen 1.5 en 2.5 gram PEG of PEG
5 blokcopolymer omvat.



RAPPORT BETREFFENDE HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK
Octrooiaanvraag 2007715

Classificatie van het onderwerp ¹ : A61K31/765, A61P35/00	Onderzochte gebieden van de techniek ¹ : A61K, A61P
Computerbestanden: EPODOC, WPI, MEDLINE, BIOSIS, TCM, EMBASE, PUBCHEM	Omvang van het onderzoek: Volledig
Datum van de onderzochte conclusies: 28 november 2011	Niet onderzochte conclusies ² :

Van belang zijnde literatuur

Categorie ³	Vermelding van literatuur met aanduiding, voor zover nodig, van speciaal van belang zijnde tekstgedeelten of figuren.	Van belang voor conclusie(s) nr.:
D, X	US 2001/0051659 A1 (ENVY ECOLE NATIONALE VETERINAIR) 13 december 2001 * het gehele document *	1-18, 20-48, 51

D, X	E. DORVAL et al. "Polyethylene glycol and prevalence of colorectal adenomas", Gastroenterol. Clin. Biol 2006, Vol. 30, pagina's 1196-1199 * het gehele document * & Samenvatting van de productkenmerken van Forlax® en Forlax® Junior * zie paragrafen 2 en 4.2 * & Samenvatting van productkenmerken van Movicol® * zie paragrafen 3 en 6 *	1-18, 20-48, 51

X	G. PARNAUD et al. "Pluronic F68 block polymer, a very potent suppressor of carcinogenesis in the colon of rats and mice", British Journal of Cancer 2001, Vol. 84 (1), pagina's 90-93 * het gehele document *	1-18, 20-48, 51

A	US 2008/0260682 A1 (ALIX PHARMACEUTICALS INC) 23 oktober 2008 * paragrafen [0047], [0054] *	1-48, 51

>> Als het gaat om octrooien

¹ Gedefinieerd volgens International Patent Classification (IPC).

² Voor motivering zie toelichting in de schriftelijke opinie.

³ Verklaring van de categorie-aanduiding: zie apart blad.

L	--- WO 2012/059725 (NORGINE BV) 10 mei 2012 -----	
Datum waarop het onderzoek werd voltooid: 6 augustus 2012		De bevoegde ambtenaar: Mw. dr. ing. L. Bechger NL Octrooicentrum

Categorie van de vermelde literatuur:

- X: op zichzelf van bijzonder belang zijnde stand van de techniek
- Y: in samenhang met andere geciteerde literatuur van bijzonder belang zijnde stand van de techniek
- A: niet tot de categorie X of Y behorende van belang zijnde stand van de techniek
- O: verwijzend naar niet op schrift gestelde stand van de techniek
- P: literatuur gepubliceerd tussen voorrangs- en indieningsdatum
- T: niet tijdig gepubliceerde literatuur over theorie of principe ten grondslag liggend aan de uitvinding
- E: octrooliteratuur gepubliceerd op of na de indieningsdatum van de onderhavige aanvraag en waarvan de indieningsdatum of de voorrangsdatum ligt voor de indieningsdatum van de onderhavige aanvraag.
- D: in de aanvraag genoemd
- L: om andere redenen vermelde literatuur
- &: lid van dezelfde octrooifamilie; corresponderende literatuur

AANHANGSEL BEHORENDE BIJ HET RAPPORT BETREFFENDE HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK, UITGEVOERD IN OCTROOIAANVRAGE NR. 2007715

Het aanhangsel bevat een opgave van elders gepubliceerde octrooiaanvragen of octrooien (zogenaamde leden van dezelfde octrooifamilie), die overeenkomen met octrooigeschriften genoemd in het rapport. De opgave is samengesteld aan de hand van gegevens uit het computerbestand van het Europees Octrooibureau per 15 augustus 2012.

De juistheid en volledigheid van deze opgave wordt noch door het Europees Octrooibureau, noch door NL Octrooiencentrum gegarandeerd; de gegevens worden verstrekt voor informatiedoeleinden.

In het rapport genoemd octrooi- geschrift		datum van publicatie	overeenkomend(e) geschrift(en)		datum van publicatie
US2001051659	A	2001-12-13	FR2784897	A	2000-04-28
			CA2347170	A	2000-05-04
			WO0024407	A	2000-05-04
			AU3528399	A	2000-05-15
			BR9914794	A	2001-07-10
			EP1124566	A	2001-08-22
			AT232390T	T	2003-02-15
			AU758348B	B	2003-03-20
			NZ511150	A	2003-03-28
			DK1124566T	T	2003-06-02
			PT1124566E	E	2003-06-30
			ES2192840T	T	2003-10-16
			DE69905384T	T	2003-11-27
US2008260682	A	2008-10-23	WO2006122104	A	2006-11-16
			CA2607250	A	2006-11-16
			AU2006244112	A	2006-11-16
			EP1877039	A	2008-01-16
			JP2008540459	A	2008-11-20
			AU2011202271	A	2011-06-09
			NZ562942	A	2012-02-24

In het rapport genoemd octrooi- geschrift		datum van publicatie	overeenkomend(e) geschrift(en)		datum van publicatie
WO2012059725	A	2012-05-10			
			NL2007715	A	2012-05-07
			BE1019494	A	2012-07-03

SCHRIFTELIJKE OPINIE
Octrooiaanvraag 2007715

Indieningsdatum:
4 november 2011

Vorrangsdatum:
4 november 2010

Classificatie van het onderwerp¹:
A61K31/765, A61P35/00

Aanvrager:
Norgine B.V.

Deze schriftelijke opinie bevat een toelichting op de volgende onderdelen:

- | | |
|--|--|
| ☒ Onderdeel I | Basis van de schriftelijke opinie |
| ☒ Onderdeel II | Vorrang |
| ☒ Onderdeel III | Vaststelling nieuwheid, inventiviteit en industriële toepasbaarheid niet mogelijk |
| ☐ Onderdeel IV | De aanvraag heeft betrekking op meer dan één uitvinding |
| ☒ Onderdeel V | Gemotiveerde verklaring ten aanzien van nieuwheid, inventiviteit en industriële toepasbaarheid |
| ☒ Onderdeel VI | Andere geciteerde documenten |
| ☐ Onderdeel VII | Overige gebreken |
| ☒ Onderdeel VIII | Overige opmerkingen |

De bevoegde ambtenaar:

Mw. dr. ing. L. Bechger

NL Octrooicentrum

¹ Gedefinieerd volgens International Patent Classification (IPC).

Onderdeel I Basis van de schriftelijke opinie

Deze schriftelijke opinie is opgesteld op basis van de meest recente conclusies ingediend voor aanvang van het onderzoek.

Onderdeel II Voorrang

Deze schriftelijke opinie is opgesteld onder de aanname dat eventueel ingeroepen voorrang geldig is, tenzij hieronder anders is aangegeven. Controleren van de voorrang maakt geen deel uit van het reguliere onderzoek naar de stand van de techniek.

Onderdeel III Vaststelling nieuwheid, inventiviteit en industriële toepasbaarheid niet mogelijk

De vraag of de uitvinding in de aanvraag nieuw, inventief en industrieel toepasbaar is, wordt niet behandeld in deze schriftelijke opinie met betrekking tot:

- ☐ de gehele aanvraag
- ☒ conclusies 49, 50

omdat:

- ☐ deze aanvraag of deze conclusies betrekking hebben op materie die geen uitvinding betreft op enig gebied van de technologie en daarom niet vatbaar is voor octrooi.
- ☒ deze aanvraag of deze conclusies betrekking hebben op materie die niet vatbaar is voor octrooi ingevolge artikel 3 van de Rijksoctrooiwet 1995.
- ☐ de beschrijving, figuren of deze conclusies, zo onduidelijk zijn dat het niet zinvol is een schriftelijke opinie op te stellen.
- ☐ een zinvolle schriftelijke opinie niet opgesteld kon worden omdat de sequentie opsomming niet beschikbaar was in het juiste formaat, of in het geheel niet beschikbaar was (WIPO ST25).
- ☐ een zinvolle schriftelijke opinie niet opgesteld kon worden zonder de tabellen met betrekking tot de sequentie opsommingen; of deze tabellen waren niet beschikbaar in elektronische vorm.

Conclusies 49 en 50 betreffen medische werkwijzen, welke volgens artikel 3, lid 1 sub f ROW 1995 (& art. 3(c), EPC 2000) niet worden beschouwd als uitvindingen die vatbaar zijn voor toepassing op het gebied van de nijverheid. Derhalve is van deze conclusies de nieuwheid en inventiviteit niet vastgesteld.

Onderdeel V Gemotiveerde verklaring ten aanzien van nieuwheid, inventiviteit en industriële Toepasbaarheid

1. Verklaring

Nieuwheid

Ja: Conclusies 1-48, 51

Schriftelijke Opinie

Octrooiaanvraag **2007715**

	Nee:	Conclusies	
Inventiviteit	Ja:	Conclusies	19
	Nee:	Conclusies	1-18, 20-48, 51
Industriële toepasbaarheid	Ja:	Conclusies	1-48, 51
	Nee:	Conclusies	

2. Literatuur en toelichting

D1 = US 2001/0051659

D2 = E. DORVAL et al. in Gastroenterol. Clin. Biol 2006

D3 = G. PARNAUD et al. in British Journal of Cancer 2001

D4 = US 2008/0260682

Conclusie 1 is geformuleerd als een tweede medische indicatie conclusie ('second medical use claim'). Zulk een conclusie maakt het mogelijk om voor een (bekende) samenstelling, waarvan een eerste geneeskundige toepassing bekend is, octrooi te verlenen voor het gebruik van dezelfde samenstelling in een tweede geneeskundige toepassing. Deze tweede geneeskundige toepassing kan de behandeling zijn van een andere ziekte maar ook een nieuw doseringsregime in de behandeling van eenzelfde ziekte (zie uitspraak van de Grote Kamer van Beroep van het EOB, **G 2/08**). Deze conclusie is pas dan nieuw als de specifiek genoemde geneeskundige toepassing (of nieuwe dosering) niet geopenbaard is in de stand van de techniek.

Nieuwheid

D1 (geciteerd in de aanvraag als corresponderend document WO 00/24407) openbaart een samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van darmkanker (CRC) in mensen, welke werkwijze het toedienen van ongeveer 20 gram PEG (polyethyleenglycol) per dag omvat.

Conclusie 1 van de onderhavige aanvraag verschilt nu daarin van D1 dat de toediening van ongeveer 800 gram of meer PEG of PEG blokcopolymeer gedurende een periode van 36 achtereenvolgende kalendermaanden plaatsvindt. Derhalve is deze conclusie nieuw.

Ook de onafhankelijke conclusies 2, 3 en 4, die respectievelijk een behandelperiode van 24 achtereenvolgende maanden, 18-36 achtereenvolgende maanden en een dagelijkse dosering van 0,1 tot 6,0 gram PEG of PEG blokcopolymeer betreffen, zijn nieuw in het licht van D1.

Onafhankelijke conclusie 29 betreft een samenstelling omvattende specifieke hoeveelheden PEG en vaste stoffen, welke hoeveelheden niet bekend zijn uit D1. Ook conclusie 29 is derhalve nieuw ten opzichte van D1.

De afhankelijke conclusies 5 t/m 28, 30 t/m 48 en 51 zijn dientengevolge ook nieuw.

Ook ten opzichte van D2 zijn de conclusies nieuw. Uit D2 volgt dat het gebruik van Forlax® (een ~10 gram PEG omvattende samenstelling, die op dagelijkse basis wordt ingenomen) gerelateerd wordt aan het

behandelen, beter maken en/of voorkomen van darmkanker. Ook uit D2 zijn echter geen specifieke gegevens bekend over de duur van toediening in combinatie met de hoeveelheid PEG (vgl. conclusie 1 e.v. van de onderhavige aanvraag).

Ook is de gewichtshoeveelheid van PEG in Forlax® (zijnde 98 gew%, berekend uit paragraaf 2 van de samenvatting van de productkenmerken van Forlax®) hoger dan de gewichtshoeveelheid in de samenstelling van conclusie 29 (50-90 gew%) van de onderhavige aanvraag.

D3 openbaart een samenstelling voor gebruik in een werkwijze voor het behandelen, beter maken en/of voorkomen van darmkanker in mensen, welke werkwijze het toedienen van ongeveer 20-40 gram Pluronic F68 blokcopolymeer (een PEG blokcopolymeer) per dag omvat. Ook uit D3 zijn geen specifieke gegevens bekend over de duur van toediening in combinatie met de hoeveelheid PEG blokcopolymeer en derhalve is D3 niet nieuwheidsbezwarend.

Inventiviteit

Conclusies 1 t/m 3 worden echter niet inventief bevonden. De doses en toedieningsduren zoals nu voorgesteld in de conclusies 1 t/m 3 zijn slechts een constatering van gegevens aanwezig in een openbare GPRD database (General Practice Research Database, zie pagina 25 van de beschrijving van de onderhavige aanvraag). Hieruit blijkt dat een totale inname van 61 - 180 zakjes Movicol® (overeenkomend met een totale hoeveelheid PEG van 800,6 – 2362,5 gram) over een periode van minimaal 24 maanden een afname in het aantal gevallen darmkanker laat zien (zie pagina 33 van de beschrijving van de onderhavige aanvraag). Conclusies 1 t/m 3 betreffende de toediening van deze totale hoeveelheden gedurende een langere periode van 24 resp. 36 achtereenvolgende maanden zijn derhalve niet inventief. Ook de maatregel van conclusie 4, betreffende een dagelijkse dosering tussen de 0,1 en 6,0 gram PEG zonder een gespecificeerde duur van toediening, is niet inventief omdat uit de beschrijving niet blijkt dat zulk een lage dosering zonder een duur van toediening daadwerkelijk effectief is.

De conclusies 5 t/m 18, 20 en 25 t/m 28 bevatten maatregelen die niet bijzonder zijn of bekend zijn uit D1, D2 of D3. Deze conclusies zijn daarom evenmin inventief.

Conclusies 21 t/m 24 betreffen de gemiddelde molecuulgewichten van de PEG, welke bekend zijn uit een van de documenten D1 of D2 en derhalve niet inventief zijn (zie paragraaf [0044] in D1 en Macrogol 3350 en Macrogol 4000 in D2).

Conclusie 29 heeft betrekking op (kort gezegd) een samenstelling voor gebruik in een werkwijze voor het behandelen van darmkanker omvattende 50-90 gew% PEG en 10-40 gew% vaste stof. De hoeveelheden en verhoudingen in deze samenstelling liggen zeer dicht bij de waardes bekend uit de literatuur (zie de samenvattingen van de productkenmerken van o.a. Forlax® en Movicol® waar respectievelijk ~98 gew% en 96 gew% PEG wordt gebruikt). Ook is mannitol een voor de vakman voor de hand liggende keuze om als vaste stof toe te passen in tabletten omvattende PEG (zie bijvoorbeeld ook paragraaf [0047] in D4), net als smaakstoffen en smeermiddelen. Als gevolg daarvan berusten conclusies 29 t/m 47 en 51 niet op uitvinderswerkzaamheid.

Conclusie 48 betreft niet meer dan een gebruikelijke stap die binnen het bereik van de vakman ligt.

Een combinatie van een lage dagelijkse dosering (0,2 tot 6,4 gram PEG of PEG blokcopolymeer, zie conclusie 13) gedurende een lange tijd (> 24 maanden), zoals beschreven in conclusie 19, wordt echter wel inventief gevonden. De totale inname van 800,6 – 2362,5 gram PEG, zoals geconstateerd in de GPRD database, vindt plaats in doses van ~13 gram PEG per keer, nl. de hoeveelheid PEG in één zakje Movicol®, zonder dat daarbij een bepaald doseringsregime is aangegeven.

In geen van de geciteerde documenten of in de GPRD database zelf wordt voorgesteld of zijn er aanwijzingen om de totale dosering van 800,6 – 2362,5 gram PEG in 24 of 36 maanden om te rekenen naar en toe te passen in genoemde lage dagelijkse dosering van 0,2 tot 6,4 gram in combinatie met deze lange toedieningsduur van 24 of 36 maanden. Deze lage dagelijkse dosering in combinatie met een lange toedieningsduur heeft als voordeel dat de dosis effectief maar niet laxatief is (zie pagina 3, regels 21-24, pagina 4, regels 25-29 en pagina 21, regels 23-27 van de beschrijving van de aanvraag).

Conclusie 19 voldoet derhalve aan de eis van inventiviteit.

Onderdeel VI Andere geciteerde documenten

Andere geciteerde openbaarmakingen

De huidige aanvraag lijkt overeen te komen met de aanvraag gepubliceerd op 10 mei 2012 onder nummer WO 2012/059725 A1, op naam van dezelfde aanvrager, terwijl de dag van indiening van de respectievelijke aanvragen dezelfde is. In art. 77 ROW 1995 is bepaald dat, in het geval dat op WO 2012/059725 A1 een Europees octrooi verleend wordt, dubbele octrooiering niet mogelijk is. Voor zover het octrooi dat verleend wordt op de huidige aanvraag betrekking heeft op dezelfde uitvinding als waarvoor aan dezelfde aanvrager een Europees octrooi is verleend, heeft het Nederlandse octrooi geen rechtsgevolgen.

Onderdeel VIII Overige opmerkingen

De volgende opmerkingen met betrekking tot de duidelijkheid van de conclusies, beschrijving, en figuren, of met betrekking tot de vraag of de conclusies nawerkbaar zijn, worden gemaakt:

De woorden “zoals”, “bij voorkeur” en “bijvoorbeeld” in de verschillende conclusies van de aanvraag zijn niet beperkend en de maatregelen in de hiernavolgende zinsneden worden dan ook niet limiterend geacht.