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Questions and answers on wheat starch (containing gluten) used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [2].

* The wording was made consistent with the food regulation (EU) No 828/2014. Please see the [corrected Annex](#) for further details.



Questions and answers on wheat starch (containing gluten) used as an excipient in medicinal products for human use

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1. What is wheat starch (containing gluten) and why is it used as an excipient?

Wheat starch is produced from wheat flour by removing proteins including gluten, meaning that wheat starch only contains trace amounts of gluten and other proteins.

Wheat starch is occasionally used as an excipient in the formulation of medicinal products such as tablets, capsules and ointments for a variety of functions: as a diluent, a disintegrant, a glidant, or as a binder. Dependent on the quality of the wheat starch, gluten can be present.

Gluten is a protein composite found in wheat and related grain species such as rye and barley.

Gluten proteins can be divided into two main groups according to their solubility in aqueous alcohols: the soluble gliadins and the insoluble glutenins. Both groups consist of numerous, closely related protein components characterised by high glutamine and proline content [4].

2. Which medicinal products contain wheat starch?

It is generally believed that only relatively few marketing authorisations (MAs) contain wheat starch throughout the EEA. For example, in the UK, a search of the MHRA database showed that there are 20 MAs that mention wheat starch as one of the excipients in the medicinal product. Most of these (n=19) are oral dosage forms and one is a topical preparation which is applied as an ointment to the skin. Similarly in several other countries and among EU centrally authorised medicines, relatively few MAs containing wheat starch were found, mainly products for oral use.

3. What are the safety concerns?

Consumption of gluten causes adverse health issues in individuals with coeliac disease (also known as coeliac sprue). Coeliac disease is caused by a reaction to components of gluten [especially the prolamin, gliadin (wheat), secalin (rye) and hordein (barley)] and probably glutenin, found in wheat, and similar proteins found in crops such as barley and rye [8–10, 26]. It is an autoimmune disorder of the digestive tract that occurs in genetically pre-disposed people of all ages from infancy.

Coeliac disease is a chronic disorder that results in an inability to tolerate gliadin. When patients with coeliac disease ingest gliadin, an immunologically mediated inflammatory response occurs that damages the mucosa of the intestines resulting in maldigestion and malabsorption [8–10, 26].

It occurs in adults and children and the rate of occurrence in the population is around 1% and prevalent all over the world [3, 6, 15, 17, 20, 22, 24, 25, 27]. In most affected people, coeliac disease remains undiagnosed [7] although the rate of diagnosis is increasing [21].

The only known effective treatment is a lifelong gluten-free diet. When a patient with coeliac disease is exposed to gluten, the patient may develop symptoms that include pain and discomfort in the digestive tract, chronic constipation and diarrhoea, failure to thrive (in children), anaemia, weight loss, weakness and fatigue, but these may be absent, and symptoms in other organ systems can develop. The extraintestinal symptoms include osteopenia, osteoporosis, skin disorders, neurological and hormonal disorders [8–10].

Upon exposure to gliadin, and specifically to three peptides found in prolamin, the enzyme tissue transglutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. That leads to a truncating of the villi lining the small intestine

(called villous atrophy). This interferes with absorption of nutrients because the intestinal villi are responsible for absorption [8–10, 21].

The total exposure needed to trigger the symptoms is not known and may differ between people. However, a review of available literature suggests that consumption of less than 10 mg of gluten per day is highly unlikely to trigger disease activity [1, 5, 11, 16, 19].

Wheat allergy is another type of immune reaction caused by allergy to one or more proteins found in wheat which is distinct from coeliac disease as it does not lead to the chronic intestinal lesions found in this autoimmune disorder.

4. What are the reasons for updating the information in the package leaflet?

Where wheat starch that contains gluten is used, it is recommended to use the same definitions for levels of gluten in medicines as described in Commission Regulation 41/2009 [13] which concerns the composition and labelling of foodstuffs suitable for people intolerant to gluten, and Commission Implementing Regulation (EU) No 828/2014 [12]. This would make it clear for people involved with or affected by coeliac disease to understand the gluten content definitions used and to take into account their total intake of gluten when taking medicine and plan their diet accordingly. According to those Regulations 'very low gluten' or 'gluten-free' is used for indicating respectively a content of gluten not exceeding 100 mg/kg and 20 mg/kg (100 ppm and 20 ppm respectively) in the final product [12, 13]. Therefore it is proposed to indicate that all medicinal products containing wheat starch as an excipient contain only very low levels of gluten (below 100 ppm) and products which contain gluten in wheat starch at levels below 20 ppm are regarded as gluten-free.

Taking into account the relatively small amount (weight) of medicinal products consumed daily compared to a daily diet, it is concluded that very low levels of gluten content in medicinal products would be acceptable, without affecting the daily diet considerations of people with coeliac disease. According to the 2003 guideline [18], if the medicinal product contains gluten, there are no requirements on the levels of gluten to be mentioned. However, as patients with coeliac disease are likely to have additional low levels of exposure to gluten in their daily diet, it is important to inform on the levels of gluten in a particular medicine to allow healthcare professionals and patients to make an informed choice. Therefore, in addition to the statement that the level of gluten in the medicine is "very unlikely to cause problems if you have coeliac disease" it is proposed to add the content of one dosage unit in x micrograms of gluten, although the name of the excipient on the packaging should remain "wheat starch".

5. Updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Wheat starch (containing gluten)	Oral	Zero	<p>This medicine contains only very low levels of gluten (from wheat starch) <. It is regarded as 'gluten-free'* > and is very unlikely to cause problems if you have coeliac disease.</p> <p>One <dosage unit> contains no more than x micrograms of gluten.</p> <p>If you have wheat allergy (different from coeliac disease) you should not take this medicine.</p> <p><i>[* The statement 'gluten-free' applies only if the gluten content in the medicinal product is less than 20 ppm.]</i></p>	The name of the excipient on the packaging should be: "Wheat starch".

Further scientific background is available in the report entitled 'Wheat starch (containing gluten) used as an excipient' [27].

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Annex 1 - Information in the package leaflet as per the 2003 Guideline [17]

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Wheat starch	Oral	Zero	<p>Suitable for people with coeliac disease.</p> <p>Patients with wheat allergy (different from coeliac disease) should not take this medicine.</p>	<p>Wheat Starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the PhEur monograph.)</p>