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Wheat starch (containing gluten) used as an excipient

Report published in support of the 'Questions and answers on wheat starch (containing gluten) used as an excipient in medicinal products for human use' (EMA/CHMP/704219/2013)

***** The wording was made consistent with the food regulation (EU) No 828/2014. Reference to the correlation between the total protein content and the gluten content has been deleted. Please see the corrected Annex for further details.

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Executive summary

This document and the related questions and answers [28] have been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' [2, 22].

It is important to provide clear information on the gluten content of medicinal products containing wheat starch for patients with coeliac disease. The gluten content is limited to 100 ppm (µg/g) when used in medicinal products.

The new information in the package leaflet requires to specify the quantitative content of gluten per tablet containing wheat starch and allows a statement of "gluten-free" when gluten concentration is less than 20 ppm in the final medicinal product, in line with the Commission Regulation on foodstuffs (41/2009) [16] and Commission Implementing Regulation (EU) No 828/2014 [15].

Introduction

Wheat starch as an excipient is found in only relatively few marketing authorisations (MAs) throughout the EEA. However, until recently, the perception has been that medicinal products containing wheat starch are gluten-free, which has been shown not to be the case using the definition in the Commission Regulation (EC) on foodstuffs (41/2009) which concerns the composition and labelling of foodstuffs suitable for people intolerant to gluten [16], calculations based on the protein content of wheat starch controlled according to the Ph. Eur. Monograph [17] and data provided from marketing authorisation holders (MAHs), although the consumption of gluten can cause adverse health issues particularly in individuals with Coeliac disease.

There are currently no clear regulatory guidelines or recommendations in place relating to the acceptable levels of gluten in medicinal products. The only guidance currently in place that indirectly mentions gluten is the Guideline on Excipients in the label and package leaflet of medicinal products for human use [21], which states that for wheat starch the information in the package Leaflet (PIL) should be 'Suitable for people with coeliac disease. Patients with wheat allergy (different from coeliac disease) should not take this medicine'. Further comments state that "wheat starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. The Ph. Eur. monograph [17] controls protein content in wheat starch to a level of NMT 0.3% (3000 ppm).

In comparison, Commission Regulation No. 41/2009 on foodstuffs [16] has defined levels of gluten for use of the terms 'gluten-free' and 'very low gluten' as not exceeding 20 ppm and not exceeding 100 ppm in the final product, respectively.

It is proposed that the PIL is in line with the Commission Regulation No. 41/2009 definitions [16] and provide clearer information on the gluten content in medicinal products containing wheat starch.

Scientific discussion

1. Characteristics

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 [5].

A search of products authorised in the UK showed that there are 20 marketing authorisations (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 skin preparation which is applied as an ointment. Similarly, in several other countries and among EU centrally authorised medicines, relatively few MAs containing wheat starch were found, mainly products for oral use.

2. Pharmaco-toxicological data

Demonstrating intolerance to gluten in animal models is difficult. The toxicity of gluten in coeliac disease stems from an immune response involving both innate and adaptive systems. In vitro and, to a lesser extent, in vivo methods have been useful in investigating the basis for gluten's immunotoxicity. Activation of CD4(+) T cells in the small intestinal mucosa by gluten peptides released by digestive enzymes is a key mechanism in coeliac disease [22]. Autoantibodies are associated with active coeliac disease and their role in pathogenesis is currently an active area of research.

The defining indicator of gluten-induced damage in coeliac disease is histopathology of the mucosa of the small intestine. It only develops in response to ongoing gluten exposure, and hence the clinical investigation of gluten intolerance faces design and ethical hurdles. No validated animal model is available to replicate the response; furthermore the heterogeneous presentation of disease hinders representative studies. However, Bethune et al were able to identify gluten-sensitive rhesus macaques (elevated anti-gliadin antibodies) and demonstrate that following alternating periods of a gluten-free diet and gluten challenge, the gluten-sensitive macaques showed signs and symptoms of coeliac disease (chronic diarrhoea, malabsorptive steatorrhoea, intestinal lesions and anti-gliadin antibodies) when fed with a gluten-containing diet [3]. These symptoms were reversible when animals were given a gluten-free diet which suggests that gluten-sensitive rhesus macaques may become a valuable resource for investigating both the pathogenesis and the treatment of coeliac disease in the future. In the absence of a validated animal model, much of the data published to date investigating the toxicity of gluten results from clinical observations.

3. Clinical safety data

Consumption of gluten causes adverse health issues in individuals with coeliac disease. Coeliac disease, also known as coeliac sprue, is an autoimmune disorder of the digestive tract that occurs in genetically pre-disposed people of all ages from infancy. It is caused by a reaction to components of gluten [especially the prolamis, gliadin (wheat), secalin (rye) and hordein (barley)] and probably glutenin, found in wheat, and similar proteins found in crops such as barley and rye [9, 10, 12, 33].

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 [9, 10, 12].

It occurs in adults and children and the rate of occurrence in the population is around 1% [6, 7, 9, 19, 34]. The disease is prevalent in Europe and in other countries of the Middle East [7, 29], Asia [31] South America [21] and North Africa [7]. In most affected people, coeliac disease remains undiagnosed [11] although the rate of diagnosis is increasing [17].

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 or diarrhoea, failure to thrive (in children), anaemia, weight loss, weakness and fatigue. However, these symptoms may be absent, and the condition may manifest itself through effects in other organ systems. The extra-intestinal symptoms include anaemia, osteopenia, osteoporosis, skin disorders, neurological and hormonal disorders [9, 10, 12].

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 [9, 10, 12, 17].

Diagnosis is by blood tests to check for relevant antibodies, followed by endoscopy/gastroscopy and biopsy. Tissue biopsy is the gold standard in the diagnosis of coeliac disease. However all tests lose their usefulness if the person has already been eating a gluten-free diet for 6–12 months. Intestinal damage begins to heal within weeks of gluten being removed from the diet, and antibody levels decline over months. In such cases, it may be necessary to perform a re-challenge with gluten-containing food in one meal a day over 6 weeks before repeating the investigations [9, 10, 12].

While the coeliac disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy, which is an immune reaction to one or more proteins found in wheat usually mediated by IgE antibodies which can present with both local and systemic manifestations.

4. Risk assessment and thresholds

The potential toxicity of gluten to coeliac patients with relation to the quantities of exposure to gluten is still unclear. The effects of a low gluten intake in coeliac disease patients have been investigated in a limited number of clinical studies. These studies all determined different acceptable limits for total gluten intake per day. Ciclitira et al analysed the toxicity and time response of a gliadin dose (the major toxic fraction of gluten) in a single patient [8]. They concluded that 10 mg produced no change, 100 mg a very slight measurable change, 500 mg a moderate change, and 1g extensive damage to small-intestinal morphology. The same group also reported that the ingestion of 2.4–4.8 mg gluten/day caused no change in the jejunal biopsy morphometry of treated coeliac disease patients after either 1 or 6 weeks. Ejderhamn et al showed that a daily intake of 4–14 mg gliadin did not affect the morphology of the small bowel mucosa in coeliac disease patients receiving long-term treatment with a gluten free diet (GFD) [17]. Recent Finnish studies [24, 27] indicate that an intake of 20–36 mg gluten/day has no detectable effect on mucosal histology. Catassi et al. showed that an intake of 50 mg gluten/day produced significant damage in the architecture of the small intestine in patients being treated for coeliac disease [6].

If the total exposure needed to trigger the symptoms remains not known, the studies mentioned above and a review of available literature suggests that consumption of less than 10 mg of gluten per day is highly unlikely to trigger perceptible disease activity and it appears that 50 mg gluten/day is the minimum dose required to produce measurable damage to the small-intestinal mucosa in coeliac disease patients [1, 6, 14, 20, 23].

5. Updated information for the package leaflet

A better understanding of the actual gluten levels in medicinal products should be made. In MAs already approved it is likely that gluten levels are confused with protein levels. Many calculations

provided assumed a gluten level of 0.3% in Ph. Eur. compliant wheat starch, however this is an incorrect assumption. The Ph. Eur. states that wheat starch should contain no more than 0.3% protein [18]. The literature reports that at levels between 0.23% and 0.34% protein, the gluten content varied between <0.01 to 0.05% [30].

The gluten content in the medicinal product may be calculated based on the quantity of wheat starch in the product. Alternatively, the gluten content in the wheat starch can be determined using a suitable analytical method. Calculation of gluten content will in practice be a 'worst-case' calculation with the assumption of maximum 100 ppm content in wheat starch as the actual gluten content may vary in wheat starch on a batch-to-batch basis.

According to the Commission Regulation 41/2009 and Commission Implementing Regulation (EU) No 828/2014 a content of gluten in foodstuffs not exceeding 100 mg/kg (100ppm) should be indicated as 'very low gluten' and a content of gluten not exceeding 20 mg/kg (20ppm) should be indicated as 'gluten-free' [15, 16]. It is therefore recommended to use the same definitions for levels of gluten in medicines as described in this Regulation. The information for the package leaflet should state 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'. 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.

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 [22], 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. As outlined previously, the level of gluten in the medicinal product can be calculated based on the level of gluten in the wheat starch excipient. Therefore, where wheat starch excipient is used in the formulation, in addition to the statement that the level of gluten in the medicine is "unlikely to cause problems if you have coeliac disease" it is proposed that the maximum possible level of gluten is determined and expressed in microgram per dosage unit. The name of the excipient on the packaging should remain "wheat starch".

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

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