Celiac disease: Understandings in diagnostic, nutritional, and medicinal aspects

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Abstract
Celiac disease (CD) is characterized by clinical polymorphism, with classic, asymptomatic or oligosymptomatic, and extra-intestinal forms, which may lead to diagnostic delay and exposure to serious complications. CD is a multidisciplinary health concern involving general medicine, pediatric, and adult gastroenterology, among other disciplines. Immunology and pathology laboratories have a fundamental role in diagnosing and monitoring CD. The diagnosis consists of serological testing based on IgA anti-transglutaminase (TG2) antibodies combined with IgA quantification to rule out IgA deficiency, a potential misleading factor of CD diagnosis. Positive TG2 serology should be corroborated by anti-endomysium antibody testing before considering an intestinal biopsy. Owing to multiple differential diagnoses, celiac disease cannot be confirmed based on serological positivity alone, nor on isolated villous atrophy. In children with classical signs or even when asymptomatic, with high levels of CD-linked markers and positive HLA DQ2 and/or DQ8 molecules, the current trend is to confirm the diagnosis on basis of the non-systematic use of the biopsy, which remains obligatory in adults. The main challenge in managing CD is the implementation and compliance with a gluten-free diet (GFD). This explains the key role of the dietitian and the active participation of patients and their families throughout the disease-management process. The presence of the gluten in several forms of medicine requires the sensitization of physicians when prescribing, and particularly when dispensing gluten-containing formulations by pharmacists. This underlines the importance of the contribution of the pharmacist in the care of patients with CD within the framework of close collaboration with physicians and nutritionists.

Keywords
Celiac disease, diagnosis, gluten-free diet, gluten-free drugs

Introduction
Celiac disease (CD) is an immune-mediated systemic disorder triggered by gluten consumption, occurring in genetically predisposed individuals.¹–³ Gluten refers to insoluble cereal proteins, including prolamins found in wheat (gliadins), rye (secalins), barley (hordein), and oats (avenins). However, the amino acid sequences inducing CD-associated immune reactions are less prevalent in avenins, which explains the tolerance of small amounts of oats by patients with CD.⁴

Unlike CD, recently described gluten sensitivity is characterized by negative serological tests and the absence of villous atrophy, and despite the

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presence of intestinal or extra-intestinal symptoms, it can be resolved by a gluten-free diet (GFD).5,6

In spite of the classical symptoms strongly suggestive of CD, the last decades have seen the emergence of asymptomatic, oligosymptomatic, or extra-intestinal often misleading forms; hence, the diagnostic delay and the risk of potentially serious complications5–10 can be avoided by implementing GFD.8,11 In addition to medical care for patients with CD, the role of the nutritionist is essential in initiating and adhering to implementing GFD. Physicians and pharmacists often fail to check for gluten when prescribing and dispensing medications; yet, it is frequently a component in the solid phase of certain galenic forms. Therefore, these drugs represent a potential source of hidden gluten.12

The aim of this review is to shed light on the diagnostic, nutritional, and medicinal aspects of CD with an emphasis on practical issues in the management of celiac patients.

### Epidemiological data

The overall prevalence of CD among the general population varies from region to region; it fluctuates between 0.5% and 1% in Europe and North America,6,13,14 and surprisingly ranges from 2% to 3% in Finland and Sweden.15 High rates are recorded in North Africa, Middle East, and Asia-Pacific regions.16 Similarly, the prevalence of the disease is reported to be high in Arab countries, reaching 3.2% in Saudi Arabia, due to dietary habits such as excessive consumption of barley and wheat, and to a higher frequency of DR3-DQ2 haplotypes.17 It is probably underestimated in South East Asia and Sub-Saharan Africa, and is almost unknown in many other countries.18

The disease is more prevalent, with large discrepancies between series in the so called high risk groups, such as type 1 diabetes (1–12%);19,20 autoimmune thyroid disease (2–6%);16,21 Down syndrome (2–6%);22,23 auto-immune hepatitis (3–7%);24,25 Turner syndrome (4–5%);26,27 CD first-degree family members (10–20%);28,29 individuals with iron deficiency anemia (3–15%);29,30 patients with osteoporosis (1–3%);29 and many other clinical conditions.16,28

In addition, The incidence of CD has significantly increased over the past 30 years, from 2–3 to approximately 9–13 new cases per 100,000 inhabitants per year.31 This likely reflects a fortuitous discovery of non-classic and asymptomatic forms of the disease through serological testing.10,13,29 Indeed, sero-epidemiological studies suggest that for each diagnosed CD case, there could be 3–7 undiagnosed cases.32

### Immunopathologic aspects

The pathogenic process of CD, as described in Figure 1, takes place in five main steps: (1) the glutamine residues of the ingested gliadin are converted into glutamates by tissue transglutaminase. (2) The modified gliadin is taken up by antigen-presenting cells carrying Human Leukocyte Antigen (HLA)-DQ2 or DQ8, thus activating gliadin-specific CD4+ T cells. (3) These cells produce pro-inflammatory cytokines, such as interleukin (IL)-15, IL-21, and interferon-gamma (IFNγ), and allow specific anti-gliadin and anti-transglutaminase responses. (4 and 5) IFNγ and IL-21 induce a massive release of IL-15, which leads to the proliferation and survival of intraepithelial lymphocytes (IEL), the activation of which alters epithelial cells, thus provoking villous atrophy.7,33

### The new face of CD

CD status has gradually changed from a rare enteropathy to a common systemic disease, and as a clinical chameleon, the CD presents in symptomatic, asymptomatic, potential, and refractory forms affecting all age groups.34

In its classic form, the disease usually starts at the age of 6 months, a few weeks after introducing gluten into the diet. It manifests as chronic diarrhea with abundant stools, accompanied by anorexia and apathy. Other clinical symptoms such as recurrent vomiting, anorexia, chronic constipation, growth or puberty delay, short stature, and irritability, are fairly characteristic and require prompt screening for the disease.35 Physical examination often shows abdominal meteorism, signs of undernutrition, loss of muscle and fat tissues, a break in the weight curve, and sometimes, slower growth in height. However, non-classic forms are more frequent than classic ones, with extra-intestinal symptoms (Table 1), thus suggesting CD.36,37 Even obese children may have CD, which undoubtedly contributes to the failure and delay of diagnosis.38

In adults, most patients with CD do not present with diarrhea, but rather “atypical or extra-intestinal”
symptoms such as anemia, osteoporosis, dermatitis herpetiformis, abdominal pain, and neurological disorders. Furthermore, in children and adults alike, serological testing should be routinely ordered in the presence of clinical conditions with a high potential for association with CD (Table 1).

**Figure 1.** Simplified immunopathological mechanism of celiac disease (adapted from7).

**Table 1.** Main circumstances justifying serological testing for CD.7,35–37,39–44

| Digestive disorders                      | Extra-digestive disorders                             | Associated pathologies                      |
|------------------------------------------|------------------------------------------------------|---------------------------------------------|
| Chronic diarrhea                         | Refractory iron deficiency anemia                    | CD in first degree relative                 |
| Irregular stools                          | Vitamin or mineral deficiencies: Vit B12, Vit B6,    | Type I diabetes                            |
| Malabsorption                            | Vit D, folate, zinc                                   | IgA deficiency                             |
| Abdominal bloating                       | Hypoplasia of tooth enamel                           | Sjogren syndrome                           |
| Chronic constipation (more common in children) | Growth retardation                                  | Autoimmune thyroiditis                      |
| Recurrent abdominal pain                 | Chronic fatigue                                       | Autoimmune liver diseases                   |
| Irritable bowel syndrome                 | Puberty delay                                         | Down syndrome                              |
| Poor weight gain                         | Amenorrhea                                            | Turner syndrome                            |
| Decreased appetite                       | Early menopause                                       | Williams syndrome                          |
| Anorexia                                  | Unexplained liver cytolysis                          | CVID (common variable immune deficiency)    |
| vomiting                                 | Bone pain, Fractures on osteopenia                    | Neurologic disorders (neuropathy, ataxia,   |
| Gastro-esophageal reflux                 | Osteoporosis                                          | migraine, epilepsy, headache, abnormal EEG*|
|                                          | Recurrent aphthous stomatitis                         | Sleep disordered breathing                  |
|                                          | Peripheral neuropathy                                 |                                            |
|                                          | Ataxia                                                |                                            |
|                                          | Unexplained hemorrhagic syndrome                      |                                            |
|                                          | Dermatitis                                            |                                            |
|                                          | Hypoplasia                                             |                                            |

*Electroencephalography abnormalities: spike/sharp wave discharges, especially in the occipital lobes and in the central-temporal sites, and in diffuse distribution.
The classical forms of CD are characterized by different laboratory findings such as anemia due to iron and/or folate deficiency, hypoprotidemia, hypoalbuminemia, decreased prothrombin time, and vitamin K-dependent factors, and lowered cholesterol mainly related to lipid leakage in the stool.\textsuperscript{46,47} In fact, biological abnormalities, such as hypocalcemia and hypophosphatemia with decreased alkaline phosphatase owing to vitamin D malabsorption, or hypertransaminasemia, may be the only suggestive signs of CD.\textsuperscript{48–50}

**Immunoserological tests**

Immunoserological tests are excellent diagnostic and monitoring tools for CD; they allow for the identification of patients at risk of developing the disease, better selection of patients requiring intestinal biopsy, and monitoring adherence to GFD.\textsuperscript{47,49,51} These tests aim to detect auto-antibodies recognizing two main antigens:

- Transglutaminase 2: targeted by anti-tissue transglutaminase 2 (anti-TG2) and anti-endomysium (EmA) Abs, which are very sensitive and specific for CD.\textsuperscript{51–54}
- Gliadin: targeted by the conventional anti-gliadin Abs, which are now obsolete owing to their low sensitivity and specificity. However, Abs against deamidated gliadin peptides (DGP) perform just as well as anti-TG2.\textsuperscript{55,56}

**Immunobiological diagnostic approach**

In daily practice, when CD is suspected, whether symptomatic or not, or in high-risk individuals, the first line of screening is based on the detection of IgA anti-TG2, followed if positive by EmA, a highly specific marker, which improves the positive predictive value (PPV) of serological tests.\textsuperscript{57–60} Indeed, the simultaneous positivity of several tests makes the diagnosis of CD very likely.\textsuperscript{61,62} In addition, a combination of IgA anti-TG2 with IgG anti-TG2 allows the exclusion of CD potentially occulted by IgA deficiency.\textsuperscript{57,58,63} Additionally, the PPV of these tests in populations at low risk for CD depends on antibody titers. Low titers (less than three times the cut-off) in asymptomatic patients should be retested after 3–6 months under a gluten-rich diet before considering endoscopy and biopsies.\textsuperscript{2,57} Moreover, the sensitivity of these tests is lower in children under 2 years of age; therefore, besides IgA anti-TG2, IgA DGP testing is recommended for this age group.\textsuperscript{39,64}

As a reproducible, non-invasive, and highly sensitive test, the salivary anti-transglutaminase testing is a promising screening tool for CD.\textsuperscript{65,66} Notably, serological tests can be falsely negative in certain circumstances as listed in Box 1.

**Box 1. Possible false negative serological tests in celiac disease.\textsuperscript{39}**

- Age <2 years
- Selective IgA deficiency
- Reduction or elimination of gluten in the diet
- Use of corticosteroids or immunosuppressive agents
- Possible laboratory error

**Rapid test screening for CD**

Physiologically present in the intracellular compartment of erythrocytes,\textsuperscript{67} TG2 made it possible to develop rapid tests based on a chromatographic method using an endogenous TG obtained from the erythrocytes of patients. However, the performance of the rapid tests remains slightly lower than that of serological tests.\textsuperscript{68,69} Several studies have demonstrated an interest in rapid tests showing a relatively good correlation with whole blood tests, and good positive and negative predictive values for ambulatory CD screening, particularly in the pediatric population.\textsuperscript{70} They could, therefore, be used for diagnostic purposes by the physician, even in an office setting.\textsuperscript{68}

**Role of the general practitioner in the management of CD**

In their daily practice, general practitioners (GP) often encounter patients with CD, regardless of their location. These doctors must rely on specific diagnostic criteria; however, this is difficult because of the wide range of clinical manifestations that patients present with.\textsuperscript{39}

GPs must know which serological screening tests to order, how to interpret the results, and which patients are to be referred to a specialist.\textsuperscript{39} Thus, according to the diagnostic algorithm proposed in Figure 2, they must refer to a pediatrician or adult gastroenterologist, any patient whose serological tests are positive, for further evaluation.
Indeed, the presence of specific antibodies in patients with CD-like symptoms is not sufficient to establish diagnosis owing to many clinical and laboratory circumstances (Box 2) mimicking CD.40,71

HLA typing
CD is linked to a strong genetic predisposition, chiefly represented by the HLA-DQ2 and DQ8 systems, which have a high negative predictive value. In fact, less than 1% of patients with CD are negative for both HLA-DQ2 and DQ8, as these are present in approximately 95% and 5% of the cases, respectively, and sometimes both molecules are found in patients.2,72,74 HLA typing cannot be performed as a CD diagnosis tool, since approximately 30–40% of the general population carry HLA-DQ2 and/or DQ8 molecules, and only about 4% of them will develop CD.74–76 On the other hand, HLA-DQ2 and DQ8 typing can be useful when the results of the biopsy are uninformative, or in patients who had initiated GFD on their own prior to serologic testing. CD can also be ruled out in symptomatic patients with negative serological tests as well as in patients considered at high risk, such as first-degree relatives of a patient with CD.74,77

Histopathological diagnosis of CD
Pathologic diagnosis is established or confirmed according to the modified Marsh-Oberhuber and Corazza-Villanacci classifications, with different scales based on the number of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy78,79 (Table 2). The Corazza score has less variability and benefits from more agreement between pathologists.77

In order to appropriately assess the histological abnormalities of CD according to commonly used criteria, it is recommended to correctly orient the endoscopic sampling (four to six staged biopsies of the bulb and/or the second duodenum) and to repeat levels of biopsy sections. In fact, an imperfectly oriented sample can give a false appearance of villous atrophy (VA).5,80
The major histological criteria of CD include VA of varying degrees with an increased number of IEL. These two signs, although nonspecific, strongly suggest CD and are associated with crypt hyperplasia and increased chorion cell density. However, VA and increased IEL can be associated with various pathologies, as listed in Box 2. In addition, patients with an isolated increase in IEL with positive serological tests are considered as potential candidates for CD as an asymptomatic latent form, while in the majority of cases, the presence of lonely intraepithelial lymphocytosis does not correspond to CD.

On the other hand, almost all VAs associated with IEL, crypt compensatory hyperplasia, chorion hypercellularity (increased density of inflammatory cells and IgA plasma cells), and positive serological tests, correspond to silent forms of CD.

### Box 2. Differential diagnoses of celiac disease.40,71–73

- Anorexia nervosa
- Autoimmune enteropathies
- Intestinal microbial swelling
- Collagen sprue
- Crohn’s disease
- Giardiasis
- HIV enteropathy
- Hypogammaglobulinemia
- Infectious gastroenteritis
- Intestinal lymphoma
- Post-radiation enteritis
- Ischemic enteritis
- Intestinal tuberculosis
- Lactose intolerance
- CVID
- IgA deficiency
- Cystic fibrosis
- Cow’s milk protein intolerance
- Tropical sprue
- Whipple’s disease
- Zollinger-Ellison syndrome
- Eosinophilic gastroenteritis
- Alpha chain disease
- Graft versus host disease
- Intestinal transplant rejection
- Malnutrition
- Enteritis (rotavirus, adenovirus, cryptosporidiosis, microsporidiosis, strongyloidosis)
- Microvillus atrophy
- Epithelial dysplasia
- Abetalipoproteinemia
- Post-drug enteropathy (ex. Olmesartan)

### Table 2. Summary of the histological classifications commonly used for CD diagnosis.72

| March modified-Oberhuber | Histological criterion | Corazza-Villanacci |
|-------------------------|------------------------|--------------------|
|                         | Increased intraepithelial lymphocytes* | Crypt hyperplasia | Villous atrophy | |
| Type 0                  | No                     | No                 | No               | None |
| Type 1                  | Yes                    | No                 | No               | Grade A |
| Type 2                  | Yes                    | Yes                | No               | |
| Type 3a                 | Yes                    | Yes                | Yes (partial)    | Grade B1 |
| Type 3b                 | Yes                    | Yes                | Yes (subtotal)   | |
| Type 3c                 | Yes                    | Yes                | Yes (total)      | Grade B2 |

*a*>40 intraepithelial lymphocytes per 100 enterocytes for Marsh Modified (Oberhuber).

*b*>25 intraepithelial lymphocytes per 100 enterocytes for Corazza.

### What can we do without the intestinal biopsy?

In children with suspected CD, the current trend is the unsystematic use of intestinal biopsy. Notably, the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition has proposed a biopsy-free approach in symptomatic children meeting the following four criteria: typical clinical signs, anti-TG2 10-fold or more the upper limit of normal (ULN), positive EmA, and positive HLA DQ2 and/or DQ8. More recently, a group of experts assume that even asymptomatic children can be accurately diagnosed with CD without biopsy, but only on basis of high titers of IgA anti-TG2 (10-fold or more the ULN), positive EmA tests on 2 blood samples. They also consider that HLA analysis is not required for accurate diagnosis. Conversely,
intestinal biopsy becomes necessary in the event of clinical manifestations suggestive of CD with negative or discordant serological tests, associated with the positivity of HLA DQ2/8 typing.\textsuperscript{2,3,7,9,0,9} In addition, patients at risk of CD with positive anti-TG2 testing cannot be exempted from the intestinal biopsy.\textsuperscript{86} In accordance with the above-mentioned guidelines, Husby et al.\textsuperscript{86} highlighted situations where intestinal biopsy is unnecessary to diagnose CD, particularly in children (Figure 3).

In all cases, the decision to perform or not biopsies in this category should be made collegially with the parent (s) and, if applicable, with the child.\textsuperscript{92}

In adults, the positivity of serological tests is insufficient to establish the diagnosis of CD, since false-positive cases are frequent in this group.\textsuperscript{93} It is, therefore, necessary to complement the serological testing with an intestinal biopsy to confirm the disease before initiating a lifelong GFD.\textsuperscript{94–96}

**Diet and gluten-free products**

GFD can only be prescribed once the diagnosis of CD has been made with certainty.\textsuperscript{97} Rigorous adherence to the GFD results in the absence of functional symptoms within a few days and rapid weight gain. The diet also leads to the decrease or even the disappearance of the VA, thus, avoiding the occurrence of complications.\textsuperscript{97}

In general, GFD consists of excluding the four categories of cereals that contain gluten and any food derived from them. Patients with CD must, therefore, systematically exclude bread, pasta, pizza, pies, cakes, and other pastries made from wheat flour as well as industrial food products and preparations, whose composition may contain gluten.\textsuperscript{98,99} Moreover, patients should be encouraged to consume whole grain gluten-free foods (e.g. quinoa, gluten-free oats, and teff) and avoid gluten-free cereals (e.g. white rice and ground corn).\textsuperscript{100}

The GFD which seems easy in theory, is in fact complicated and difficult to follow, especially in nurseries and schools, restaurants, and even at home.\textsuperscript{101} Gastroenterologists, pediatricians, and GPs must therefore convince the patient to follow this diet and emphasize the importance of its lifelong compliance.\textsuperscript{97,98} In this regard, the involvement of the dietitian in the care of patients with CD is fundamental.
When to refer a patient with CD to a dietitian

After confirmation of CD, the clinical conditions listed below (Box 3) require a systematic referral of the patient to an experienced dietitian as part of a collaborative approach.

Role of the dietitian in the care of a patient with CD

The initiation of a GFD should preferably be entrusted to an experienced dietitian who is perfectly familiar with this type of diet that requires clear and detailed explanations, with particular attention to its pitfalls.9,100

During the first consultation, the dietitian explains the GFD and insists on the importance of complete and definitive exclusion of gluten from the diet.97,98

The ubiquitous character of gluten in foods requires providing the patients and their families with the most exhaustive possible list of authorized and prohibited foods. Table 3 presents the main categories of foods containing gluten that the dietitian should explain to the celiac patient and/or to his family.

At the second consultation (scheduled 1 month after the first), the dietitian will answer questions related to any difficulties the patient may encounter, and ensure that a balanced diet is maintained and the weight is regained. The dietitian must also inquire about the social integration of the patient into the new lifestyle, and about the implementation of meals, particularly in nurseries, schools, and in the workplace.

The following consultations are usually coupled with a medical follow-up of the patient at 3 and 6 months, and then once a year. However, they can be more frequent depending on patient needs.98

To ensure smooth progress of GFD, the dietitian is in charge of educating the patient or his family to:

1- Avoid the risk of contamination by gluten-containing products through the following precautions:

- Gluten-free products should be meticulously separated from those containing gluten, reserving an appropriate space in the pantry and the refrigerator
- Work surfaces, appliances, toasters or bread makers, cooking utensils, and dishes used to prepare other meals should be thoroughly cleaned before use, or should preferably not be used
- Frying baths should only be used for breaded products or donuts.97,100,102

2- Read the product labeling carefully:

Patients with CD should be encouraged to routinely read product labels to check for the presence of cereals containing gluten; some ingredients may even change over time. It is also necessary to be vigilant toward foods sold in bulk or catering products.99,103

In addition, terms found on the labels of many products indicate that some ingredients contain gluten and should not be consumed; for example, starch from wheat, barley, rye, or oats; unleavened bread (wheat flour); kamut (ancient wheat), bulgur; malt, and others. A precise list of terms appearing in the composition of a product, which indicate the presence or absence of gluten must also be made available to the patients and their families.4,97,103 A comprehensive list of ingredients and additives that may contain gluten is provided in Table 4, making it easy to identify gluten in food products through their labels.

Medical follow-up for patients with CD

A strict follow-up and a multi-disciplinary approach are needed to ensure harmonious growth
Table 3. List of allowed and prohibited foods for celiac disease.4,99,102

| Food                   | Allowed                                                                 | Prohibited                                                                 |
|------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Milk and dairy products| Whole milk, semi-skimmed, skimmed, growth milk                          | Flavored milk                                                               |
|                        | Sweetened or unsweetened condensed milk                                 | Cereal and fiber yogurts and dairy products                                |
|                        | Fresh, pasteurized, powder, UHT sterilized milk                         | Fruit yogurts                                                              |
|                        | Goat and sheep milk                                                     | Fool Epi Cheese                                                            |
|                        | Plain fermented milk                                                    | Industrial milk-based preparations (custards, creams, gelling agents, desserts, foam, etc.) |
|                        | Yogurts, flavored white cheeses                                          | Mold and spread cheeses                                                    |
|                        | Soft, hard, cooked, melted cheeses                                       | Cereal-based dairy desserts                                                |
| Meats                  | All fresh meats, natural frozen, or natural canned                      | Commercial ready-made preparations based on meat or poultry                 |
|                        | Ground beef “pure beef”                                                 | Breaded, crusted, or flaky preparations                                     |
| Eggs                   | All                                                                     | Industial scrambled eggs                                                   |
| Fish                   | All fresh, smoked, frozen fish, canned fish                             | Breaded or floured fish                                                    |
|                        | Natural crustaceans and mollusks                                        | Commercial preparations based on fish or fish butter                       |
|                        | Fish roe                                                                | Fish dumplings                                                             |
|                        |                                                                         | Surimi                                                                      |
| Cold meat              | White ham or country ham                                               | Breaded ham                                                                |
|                        | Cooked shoulder                                                        | Meat stuffing                                                              |
|                        | Unbreaded ham                                                          | Foams and foie gras cream                                                  |
|                        | Salted or smoked breast, bacon                                         | Dough and galantine                                                       |
|                        | Rillettes                                                              | Pies, sweets, quiches, queen bites                                         |
|                        | Candied and natural foie gras                                          | Dry sausages                                                               |
|                        | Plain sausage meat                                                     | Garlic sausages, dry sausages, salami, chorizo, cervelas, dumplings        |
|                        | Sausages from Strasbourg, Morteau, Frankfurt, Montbéliard              | White and Caribbean sausages                                               |
|                        | Mortadella, head cheese, snout                                          | Black pudding                                                             |
|                        | Andouille and andouillette                                              |                                                                            |
| Cereals and starchy foods | Rice and rice products: rice cream, pure rice semolina, rice cakes     | Wheat or wheat, rye, barley, oats, spelled, kamut, triticale, and their derivatives: |
|                        | Corn and derivatives: maizena, semolina                                | - Flour                                                                   |
|                        | - Cassava and derivatives: tapioca, tapiocaline                         | - Semolina                                                                 |
|                        | Buckwheat and pure buckwheat flour (without wheat flour)               | - Pasta, vermicelli, ravioli, gnocchi                                      |
|                        | Soy and soy flour                                                      | - Bulgur                                                                   |
|                        | Sorghum                                                                | - Flakes                                                                   |
|                        | Millet                                                                 |                                                                            |
|                        | Sesame                                                                 |                                                                            |
|                        | Quinoa                                                                 |                                                                            |
|                        | Maranta                                                                |                                                                            |
|                        | Sweet potatoes                                                         |                                                                            |
|                        | Yam                                                                    |                                                                            |
|                        | Plantain                                                               |                                                                            |
|                        | Gluten-free infant flour                                               |                                                                            |
|                        | Certain breakfast cereals made only from rice and/or corn and without malt |                                                                            |

(Continued)
| Food                        | Allowed                                                                 | Prohibited                                                                 |
|-----------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Vegetables and dried        | - Potato and potato starch                                              | - All commercial cooked vegetables (canned, frozen, catering)              |
| vegetables                  | - All fresh green vegetables, canned or frozen naturally, cooked under a vacuum | - Soups in sachets or in boxes                                             |
|                             | - All dried vegetables                                                  | - Dauphine potatoes, duchess potatoes (check the coating of the hazelnut apples and pre-cooked fries) |
|                             | - Small jars of homogenized vegetables mentioned gluten-free           | - Flavored crisps                                                          |
| Fruits                      | - Fresh or natural frozen fruit                                         | - Instant mashed potato                                                    |
|                             | - Fruits in syrup                                                       | - Dried figs (flour that can be used for drying)                           |
|                             | - Frozen or canned compotes                                             | - Glazed chestnuts and candied fruit (handling possible with floured fingers) |
|                             | - Chestnuts, natural chestnuts                                          | - Dry grilled oil seeds                                                    |
|                             | - Oilseeds not dry roasted (nuts, hazelnuts, peanuts, almonds)          |                                                                             |
|                             | - Small jars of homogenized fruit without cereals                       |                                                                             |
| Fat                         | - Oil, butter, fresh cream, Vegetal, margarine, Bacon, bacon, tallow, goose fat | - Wheat germ oil                                                           |
| Sweet products              | - White sugar, brown sugar, cane, vanilla                               | - Low-fat butters or margarines                                            |
|                             | - Jelly, jam, pure fruit chestnut cream                                 | - Nougat                                                                   |
|                             | - Honey                                                                 | - Sugared                                                                  |
|                             | - Pure, tablet, dark, or milk chocolate                                | - Banania chocolate powder                                                |
|                             | - Pure cocoa                                                            | - All loose candy                                                          |
|                             | - Sour candies and lollipops                                             | - Eskimos and ice cream in cornet                                           |
|                             | - Pure vanilla extract                                                  | - Packaged candy                                                           |
|                             | - Pure licorice                                                         | - Commercial ice creams and sorbets                                         |
| Drinks                      | - Tea, coffee, chicory, infusions                                       | - Filled chocolates                                                        |
|                             | - Fruit juice, fruit syrup                                              | - Chocolate powders                                                       |
|                             | - Sodas and lemonade                                                    | - Icing sugar                                                              |
| Condiments and various      | - Aromatic herbs, pure spices, salt, pepper                            | - Chocolate powders                                                       |
|                             | - Garlic, onion, shallot, pickle                                        | - Spice mixes                                                              |
|                             | - Some mustards                                                        | - All other commercial condiments and sauces                               |
|                             | - Baker’s yeast                                                        | - (Curry, soy sauce, mayonnaise, etc.)                                    |
|                             | - Sodium carbonate to replace baking powder                             | - Savora mustard                                                           |
|                             |                                                                        | - Baking powder                                                            |
and prevent CD-related complications. As summarized in Table 5, the medical follow-up is generally based on clinical evaluation, serological testing, nutritional assessment, bone density measurement, liver and thyroid exploration, intestinal biopsy and cancer screening.

Patients with CD should be examined at least twice during the first year after diagnosis, to monitor clinical and biological manifestations, nutritional status, body mass index (BMI), serological tests, and to assess compliance with GFD. BMI can be a reliable reflection of the impact of GFD on the nutritional status of celiac patients: underweight patients typically gain weight and overweight or obese patients lose weight. The efficiency of a GFD is thus attested by clinical and biological improvement (1–3 months), the negativity of specific Ab tests, and the regression of histological abnormalities (12 months). Regular monitoring of serology makes it possible to detect diet deviations, whether voluntary or not; and patients whose serological tests do not improve should be reassessed for continued exposure to gluten.

One of the most controversial aspects of CD is the value and the timing of the intestinal biopsy when monitoring the disease. To better appreciate the evolution of intestinal damage, a biopsy is generally recommended 1–2 years after GFD initiation. However, intestinal healing is often slow, incomplete, and age-dependent. Moreover, intestinal biopsy remains essential if symptoms persist.

In general, the management of CD must include a nutritional assessment in order to detect deficiencies such as autoimmune thyroiditis (T3, T4, TSH,
anti-thyroperoxidase, and anti-thyroglobulin antibodies) and justify replacement therapy (hemoglobin, albumin, calcium, folate, vitamin B12, zinc, magnesium, and vitamin D).\(^9\)

It is also recommended to evaluate bone mineral density during the first year of follow-up, using densitometry.\(^9,72\)

In the pediatric population, the late childhood is particularly critical for the conduct of GFD. In fact, this diet impacts daily life and can be a source of frustration or even depression, and often experienced as “dissocializing,” especially among adolescents.\(^101,108\) Closer follow-up by both the specialist and the dietitian is, therefore, necessary to re-explain the disease and its complications, to understand the difficulties of the adolescent in accepting the diet, and to help them overcome social or academic constraints, thus, preventing potential abandonment of the diet.\(^109\)

On the other hand, the transition to adulthood is often a period of slackening during follow-up, and sometimes of GFD. Consequently, the orientation toward the adult specialist becomes necessary to ensure continuity in care and avoid the insidious installation of serious complications, mainly, osteopenia and fracture osteoporosis, increased risk of autoimmune diseases (type I diabetes, thyroiditis, and others), hypofertility, or even sterility, neuropathies, and particularly the risk of cancers such as adenocarcinomas and intestinal lymphomas.\(^3,11,108\)

Medicines are a potential source of gluten concealment, which is commonly introduced into the solid phase of drugs such as tablets and pills when the starch used is extracted from wheat, rye, and/or barley, serving as a diluent or binder.\(^12,103\) Starch is also used as a carrier for controlled or sustained-release dosage forms as well as to form nanoparticles, nanogels, and microcapsules.\(^110\) The excipients of some drugs may also contain gluten in small quantities, especially those based on wheat starch, wheat germ oil, wheat bran, wheat flour, barley bran, and vegetable amylase, which can be extracted from barley.\(^104\) The type of excipients can also be different between generic and branded drugs, and those with a known effect (lactose and gluten) must be indicated in the leaflet intended for patients.\(^111\) Thus, even if the brand name is

| Table 5. Guidelines for medical monitoring of patients with celiac disease.\(^40\) |
|-----------------|-----------------|-----------------|
| Test            | Time interval   | Comments                     |
| Clinical evaluation | Annually or if recurring symptoms | Normal titers are insensitive to continuous exposure to gluten or enteropathy. The continuous increase in titers indicates significant exposure to gluten. |
| Serology        | Every 3–6 months until normalization Then every 1–2 years | Iron deficiency, 25-OH vitamin D, vitamin B12, folate, and zinc. Monitoring of weight gain, low fiber intake, and constipation. |
| Nutritional assessment | Every 3–6 months until normalization Then every 1–2 years | Significant increases in bone density are often seen during the first year after diagnosis. Several experts therefore recommend the test 1 year after the GFD. |
| Bone density    | Once during the first 2 years | |
| Liver transaminases (ALT/AST) | At the time of diagnosis Then every 1–2 years | Increased levels of ALT and AST are common during celiac disease. Their constant increase indicates an associated hepatic co-morbidity. |
| Functional exploration of the thyroid | At the time of diagnosis Then every 1–2 years | Autoimmune thyroiditis is the most common autoimmune disorder found in approximately 15%–20% of celiac adults. |
| Intestinal biopsy | To be considered 1–2 years after diagnosis | Repeated biopsies to assess healing are frequently performed. However, their interest remains controversial in celiac patients responding well to GFD with a good clinical course. |
| Cancer screening | As for the general population | Even if the rate of certain cancers is high, they are not frequent enough to justify a specific systematic screening. |
determined to be gluten-free, the gluten-free status of each generic must be verified by the pharmacist and the celiac patient as well.

Unfortunately, drug manufacturers may not disclose the source of the starch used or indicate whether their products are free from gluten contamination.\textsuperscript{12} Indeed, all medicines can be made gluten-free since alternatives to starch can be used during production. This highlights the importance of adopting a new policy for the manufacture of gluten-free drugs by pharmaceutical companies and excipient producers.\textsuperscript{12}

Since 2017, Food and Drug Administration (FDA) has issued a draft guidance on Gluten in Drug Products and Associated Labeling, recommending to drug manufacturers a statement to include in their labeling when truthful and properly supported: “Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)”.\textsuperscript{112}

Hence, the pharmacist has an essential role in the management of gluten-intolerant patients. He must check whether the medicine contains gluten, even in very small quantities, especially in excipients. The following components indicate the presence of gluten in the drug: starch, glycerol starch, starch glycolate, carboxymethyl starch, partial hydrolysate of hydrogenated starch, modified/soluble/pregelatinized starch, precooked/processed wheat germ oil, wheat bran, barley, and vegetable amylase. An exception is made for the specialties of Maxilase\textsuperscript{®} or Megamylase\textsuperscript{®} (possibly extracted from barley), which have been authorized by the French association of gluten intolerants after investigations in pharmaceutical laboratories.\textsuperscript{113}

Box 4 reports a non-exhaustive list of medications containing gluten, drawn from the Vidal dictionary, indicating both the generic and the brand name. A complementary list of drugs that may or may not contain gluten depending on the concentration and formulation of the drug is displayed in Table 6. Indeed, the generic name of drugs may differ depending on the country of origin and distribution. These lists must also be regularly updated with the development of new generic drugs. Thus, both pharmacists and patients with CD should constantly check the composition of the drugs.\textsuperscript{113} Determining the gluten status of generic drugs is challenging owing to changes in manufacturers, drug shortages, and wholesale product variability. These factors make identifying the gluten content in generic medications difficult, even for the manufacturers themselves.\textsuperscript{114}

Additionally, even low gluten intake can irritate sensitive individuals.\textsuperscript{104} In contrast, the ointment forms, effervescent tablets, drinkable drops, oral solutions, eye drops, suppositories, nasal drops, and injectable ampoules are gluten-free regardless of the specialty name.\textsuperscript{113} Some medications are the only ones to contain the active principle, and the benefit/risk ratio of these drugs must therefore be evaluated by the prescriber before use or exclusion in any therapy.\textsuperscript{104,114}

To sum up, this overview suggested an integrated approach to the main practical aspects of CD (clinical and laboratory diagnosis; implementation and monitoring of gluten-free diet; delivering and use of gluten-free medications), which represent concerns for physicians, biologists, nutritionists and pharmacists during the process of CD management. However, as limitations, some aspects have not been or insufficiently developed, such as the role of innate immunity in the pathogenesis of CD, the comparative performance of serological testing, the seronegative and refractory CD and possible immunotherapeutic approaches. We have also been faced to the scarcity of scientific data related to drugs and gluten.

**Conclusion**

Despite its polymorphism with many differential diagnoses, CD benefits from a standardized diagnostic approach based on serology, intestinal biopsy, and possibly HLA typing. The management of CD is a multidisciplinary concern, involving general practitioners, different clinical and biological specialists, as well as dietitians and pharmacists.

The implementation and monitoring of GFD remains a challenge, which reflects the incontestable role of the dietitian as well as that of the pharmacist, considering the risk of the existence or concealment of gluten in the various stages of drug manufacturing.

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**Box 4.** Pharmaceutical specialties containing gluten or marked “wheat starch” in their composition.104,113 (Brand names of drugs are put between brackets).

- ABUFENE (Beta-alanine) 400 mg tablet
- ACETOBUTOLOL WINTHROP (acebutolol) 200 mg coated tablet
- ACETOBUTOLOL ZENTIVA (acebutolol) 400 mg coated tablet
- ADENYL (Adenosine phosphate) 60 mg tablet
- ADIAZINE (Sulfadiazine) 500 mg tablet
- ALFATIL (Cefaclor) 250 mg/5 ml powder for oral suspension
- ALLOPURINOL ARROW (allopurinol) 100 mg tablet
- ALLOPURINOL ARROW (allopurinol) 200 mg tablet
- ALLOPURINOL ARROW (allopurinol) 300 mg tablet
- ALLOPURINOL EG (allopurinol) 100 mg tablet
- ALLOPURINOL EG (allopurinol) 300 mg tablet
- ALLOPURINOL SANDOZ (allopurinol) 100 mg tablet
- ALLOPURINOL SANDOZ (allopurinol) 200 mg tablet
- ALLOPURINOL SANDOZ (allopurinol) 300 mg tablet
- APAROXAL (phenobarbital) 100 mg tablet
- ARTANE (trihexyphenidyl hydrochloride) 2 mg tablet
- ARTANE (trihexyphenidyl hydrochloride) 5 mg tablet
- ARTICHAUD BOIRON (Cynara scolymus) capsule
- ATHYMIL (mianserin hydrochloride) 10 mg coated tablet
- ATHYMIL (mianserin hydrochloride) 30 mg coated tablet
- ATHYMIL (mianserin hydrochloride) 60 mg coated tablet
- ASPIRINE RICHARD (aspirin) 500 mg tablet
- BECILAN (pyridoxine hydrochloride) 250 mg coated tablet
- BEVITINE (thiamine hydrochloride) 250 mg coated tablet
- BI-PROFENID LP (ketoprofen) 100 mg tablet
- BOURDAINE BOIRON (Frangula alnus) capsule
- BUFLOMEDIL ARROW (buflomedil) 150 mg tablet
- BUFLOMEDIL ARROW (buflomedil) 300 mg tablet
- BUFLOMEDIL EG (buflomedil) 150 mg coated tablet
- BUFLOMEDIL EG (buflomedil) 300 mg coated tablet
- BUFLOMEDIL GNR (buflomedil) 150 mg tablet
- BUFLOMEDIL GNR (buflomedil) 300 mg tablet
- BUFLOMEDIL IREX (buflomedil) 150 mg tablet
- BUFLOMEDIL IREX (buflomedil) 300 mg tablet
- BUFLOMEDIL RPG (buflomedil) 150 mg tablet
- BUFLOMEDIL RPG (buflomedil) 300 mg tablet
- BUFLOMEDIL RATIOPHARMA (buflomedil)
- BUFLOMEDIL TEVA (buflomedil) 150 mg coated tablet
- BUFLOMEDIL TEVA (buflomedil) 300 mg tablet
- BUFLOMEDIL ZYDUS (buflomedil) 150 mg tablet
- CANTABILINE (Hymecromone) 400 mg tablet
- CERIS (trosiptum chloride) 20 mg coated tablet
- CASSIS BOIRON (Ribes nigrum) capsule
- CLARITHROMYCINE SANDOZ (clarithromycin) 50 mg/ml powder for oral suspension
- CHLORHYDRATE D'HEPTAMINOL RICHARD (Heptaminol hydrochloride) 187.8 mg tablet
- CIRKAN (Hesperidin Methyl Chalcone) coated tablet
- COLIMYCINE (colistimethate sodium) 1.5 M UI tablet
- CYNOMEL (liothyronine sodium) 25 μg tablet
- DANTRIUM (dantrolene sodium) 100 mg capsule
- DANTRIUM (dantrolene sodium) 25 mg capsule
- DENSICAL VITAMINE D3 (cholecalciferol) powder for oral suspension
- DESINTEX (sodium thiosulphate) coated tablet
- DEXAMBUTOL (ethambutol) 500 mg coated tablet
- DIAMOX (acetazolamide) 250 mg tablet
- DICYNONE (tranexamic acid) 500 mg tablet
- DI-HYDAN (phenytoin sodium) 100 mg tablet

(Continued)
Box 4. (Continued)

- DISULONE (dapsone) tablet
- DOLIPRANE LIB (paracetamol) 500 mg tablet
- DOLIRHUME (paracetamol + pseudoephedrine) 500 mg/30 mg tablet
- DOLIRHUMEPRO (paracetamol, pseudoephedrine & doxylamine) tablet
- DOXYLAMINE (doxylamine) tablet
- ENTECET (germinated barley + amylase) coated tablet
- ENTEROPATHYL (sulfaguanidine) 500 MG
- ENZYMICINE (Neomycin) cone for dental use
- ESIDREX (hydrochlorothiazide) 25 mg tablet
- EXACYL (tranexamic acid) 500 mg coated tablet
- FAGOPYRUM ESCULENTUM
- FLAGYL (metronidazole) 250 mg coated tablet
- FLAGYL (metronidazole) 500 mg coated tablet
- FURADANTINE (nitrofurantoin) 50 mg capsule
- FURADOINE (nitrofurantoin) 50 mg tablet
- GARDENAL (phenobarbital) 10 mg tablet
- GARDENAL (phenobarbital) 50 mg tablet
- GARDENAL (phenobarbital) 100 mg tablet
- GINSENG BOIRON (ginseng) capsule
- GLUTAMINOL B6 (glutamic acid + Pyroxidine) tablet
- HEPTAMYL 187.8 (heptaminol) mg tablet
- HEXASTAT (altrétamine) 100 mg capsule
- IMOVANE (zopiclone) 3.75 mg coated tablet
- IMOVANE (zopiclone) 7.5 mg coated tablet
- INSADOL (corn) 35 mg coated tablet
- ISOPRINOSINE (inosine acedoben dimepranol) 500 mg tablet
- KETOPROFENE ZENTIVA LP (ketoprofen) 100 mg tablet
- LARGACTIL (chlorpromazine hydrochloride) 100 mg coated tablet
- LARGACTIL (chlorpromazine hydrochloride) 25 mg coated tablet
- LEGALON (silymarin) 70 mg coated tablet
- LIORESAL (baclofen) 10 mg coated tablet
- MALOCIDE (pyriméthamine) 50 mg tablet
- MEGAMAG (magnesium) 45 mg capsule
- MEPROBAMATE RICHARD (meprobamate) 400 mg tablet
- METHOTREXATE BELLON (methotrexate) 2.5 mg tablet
- MODUCREN (timolol maleate + amiloride chlorhydrate + hydrochlorothiazide) tablet
- MUCITUX (eprazinone dihydrochloride) 50 mg coated tablet
- NEO-CODION (codeine) coated tablet
- NEOCONES (neomycin sulfate + benzocaine) cone for dental use
- NEULEPTIL (propériciazine) 25 mg coated tablet
- NIVAQUINE (Chloroquine) 100 mg tablet
- NORDAZ (Nordazepam) 15 mg tablet
- NORDAZ (Nordazepam) 7.5 mg tablet
- NOTEZINE (diethylcarbamazine) 100 mg tablet
- NOZINAN (levomepromazine) 100 mg coated tablet
- NOZINAN (levomepromazine) 25 mg coated tablet
- PARACETAMOL SANDOZ (paracetamol) 1 g tablet
- PARACETAMOL SANDOZ (paracetamol) 500 mg tablet
- PARACETAMOL ZYDUS (paracetamol) 500 mg tablet
- PASSIFLORE BOIRON (passiflora) capsule
- PEFLACINE (pefloxacin) 400 mg coated tablet
- PEFLACINE MONODOSE (pefloxacin) 400 mg coated tablet
- PERUBORE INHALATION (plant essences) inhalation tablet
- PHENERGAN (promethazine) 25 mg coated tablet
- PHOLCODYL (pholcodine) liquid mixture
- PIPORTIL (pipotiazine) 10 mg coated tablet
- PIPRAM FORT (piperacillin + tazonactum) 400 mg coated tablet
- PRAZINIL (carpipramine) 50 mg coated tablet
- PREVISCAN (fluindione) 20 mg tablet
- PROFEMIGR (ketoporofen) 150 mg tablet

(Continued)
Table 6. Gluten status of medications (adapted from114).

| Drug (Manufacturer) | Strength and formulation | Gluten status |
|---------------------|--------------------------|---------------|
| Allopurinol (Mylan) | 300 mg tablet            | Gluten free   |
| Amino acid solution (B. Braun) | 10% and 15% injections | Gluten free   |
| Azacitadine (Celgene) | 100 mg injection | Gluten free   |
| Barium sulfate contrast dye (EZ EM CANADA) | 9.5 g in 23.5 g suspension | Gluten free   |
| Dextrose solution (Hospira) | 5% injection | Gluten free   |
| Diphenoxylate /atropine (Mylan) | 2.5 mg/0.025 mg tablet | Gluten free   |
| Doxycycline hyclate (Mylan) | 100 mg tablet | Gluten free   |
| Endure handsoap (Ecolab) | Not applicable | Gluten free   |
Table 6. (Continued)

| Drug (Manufacturer)                        | Strength and formulation          | Gluten status        |
|--------------------------------------------|-----------------------------------|----------------------|
| Levocetirizine (Dr. Reddy’s)               | - 5 mg tablet                     | - Gluten free        |
| Linezolid (Pfizer)                         | - 100 g/5 mL suspension           | - Gluten free        |
| Lipid emulsion (Fresenius kabi)            | - 10%, 20%, and 30% injections    | - Gluten free        |
| Loperamide (Mylan)                         | - 2 mg capsule                    | - Gluten free        |
| Losartan (Mylan)                           | - 25 and 50 mg tablets            | - Gluten free        |
| Magnesium oxide (McKesson Packaging)       | - 400 mg tablet                   | - Gluten free        |
| Menthol/camphor (Geritrex)                | - 0.5%/0.5% lotion                | - Gluten free        |
| Metaxalone (Amneal)                        | - 800 mg tablet                   | - Gluten free        |
| Morphine (Hospira)                         | - 2 and 4 mg injections           | - Gluten free        |
| Pomalidomide (Celgene)                     | - 1, 2, 3, and 4 mg capsules      | - Gluten free        |
| Prochlorperazine (Mylan)                   | - 5 mg tablet                     | - Gluten free        |
| Rosuvastatin (AstraZeneca)                 | - 5, 10, 20, and 40 mg tablets    | - Gluten free        |
| Salsalate (Amneal)                         | - 500 and 750 mg tablets          | - Gluten free        |
| Acetaminophen (McNeil)                     | - 325 mg tablet                   | - Possibly contains gluten |
| Acetaminophen (McNeil)                     | - 500 mg caplet                   | - Possibly contains gluten |
| Acyclovir (Teva)                           | - 200 mg capsule                  | - Possibly contains gluten |
| Acyclovir (Teva)                           | - 400 mg tablet                   | - Possibly contains gluten |
| Allopurinol (Watson)                       | - 300 mg tablet                   | - Possibly contains gluten |
| Amlodipine (Teva)                          | - 5 mg tablet                     | - Possibly contains gluten |
| Amoxicillin (Sandoz)                       | - 400 mg/5 mL suspension          | - Possibly contains gluten |
| Amoxicillin/clavulanate (Sandoz)           | - 500 and 875 mg tablets          | - Possibly contains gluten |
| Aripiprazole (Otsuka)                      | - 2, 5, 10, 15, 20, and 30 mg tablets | - Possibly contains gluten |
| Atazanavir (Bristol-Meyers Squibb)         | - 150, 200, and 300 mg capsules   | - Possibly contains gluten |
| Butalbital/acetaminophen/caffeine (Qualitest) | - 325 mg/50 mg/40 mg tablet      | - Possibly contains gluten |
| Celecoxib (Pfizer)                         | - 50, 100, 200, and 400 mg capsules | - Possibly contains gluten |
| Cephalaxin (Teva)                          | - 500 mg capsule                  | - Possibly contains gluten |
| Ciprofloxacin (Watson)                     | - 250 and 500 mg tablets          | - Possibly contains gluten |
| Clindamycin (Watson)                       | - 150 mg capsule                  | - Possibly contains gluten |
| Dabigatran (BoehringerIngelheim)           | - 75 and 150 mg capsules          | - Possibly contains gluten |
| Darunavir (Janssen)                        | - 75, 150, 400, 600, and 800 mg tablets | - Possibly contains gluten |
| Darunavir (Janssen)                        | - 100 mg/mL suspension            | - Possibly contains gluten |
| Dextran/hydroxypropyl methylcellulose (Alcon) | 0.1%/0.3% ophthalmic solution     | - Possibly contains gluten |
| Diphenhydramine (Major)                    | - 25 and 50 mg tablets            | - Possibly contains gluten |
| Diphenhydramine (Qualitest)                | - 12.5 mg/5 mL liquid             | - Possibly contains gluten |
| Diphenoxylate/atropine (Greenstone)        | - 2.5 mg/0.02 mg tablet           | - Possibly contains gluten |
| Emtricitabine/tenofovir (Gilead)           | - 200 mg/300 mg tablet            | - Possibly contains gluten |
| Ethinyl estradiol/levonorgestrel (Watson)  | - 0.03 mg/0.15 mg tablet          | - Possibly contains gluten |
| Ethinyl estradiol/norethindrone (Watson)   | - 0.035 mg/l mg tablet            | - Possibly contains gluten |
| Ethinyl estradiol/norgestimate (Janssen)   | - Varies                          | - Possibly contains gluten |
| Ethinyl estradiol/norgestimate (Watson)    | - Varies                          | - Possibly contains gluten |
| Ethinyl estradiol/norgestrel (Watson)      | - 0.03 mg/0.3 mg tablet           | - Possibly contains gluten |
| Estravirine (Janssen)                      | - 25, 100, and 200 mg tablets     | - Possibly contains gluten |
| Fluconazole (Teva)                         | - 400 mg tablet                   | - Possibly contains gluten |
| Hydrocortisone cream (Fougera)             | - 0.5% cream                      | - Possibly contains gluten |
| Hydrocortisone cream (Wyeth)               | - 1% cream                        | - Possibly contains gluten |
| Hydrocortisone sodium succinate (Pfizer)   | - 100 mg injection                | - Possibly contains gluten |
| Intravenous immune globulin (CSL Behring)  | - 3, 6, and 12 g injections       | - Possibly contains gluten |
| Levofloxacin (Lupin)                       | - 250 and 500 mg tablets          | - Possibly contains gluten |
| Linezolid (Pfizer)                         | - 600 mg tablet                   | - Possibly contains gluten |
| Lopinavir/ritonavir (AbbVie)               | - 100 mg/25 mg and 200 mg/50 mg   | - Possibly contains gluten |
| Lopinavir/ritonavir (AbbVie)               | - 80 mg/20 mg/mL solution         | - Possibly contains gluten |
| Magnesium trisalicylate (Silarx)           | - 500 mg solution                 | - Possibly contains gluten |
| Maraviroc (ViiV Healthcare)                | - 150 and 300 mg tablets          | - Possibly contains gluten |
| Multivitamin with fluoride (Qualitest)     | - 0.25, 0.5, and 1.0 mg chewable tablets | - Possibly contains gluten |
| Nimodipine (Arbor)                         | - 3 mg/mL solution                | - Possibly contains gluten |

(Continued)
Table 6. (Continued)

| Drug (Manufacturer)                                      | Strength and formulation | Gluten status               |
|----------------------------------------------------------|--------------------------|------------------------------|
| - Oxycodone immediate release (Actavis)                  | - 15 and 30 mg tablets   | - Possibly contains gluten   |
| - Pantoprazole (Dr. Reddy’s)                             | - 20 and 40 mg tablets   | - Possibly contains gluten   |
| - Potassium chloride (Upsher-Smith)                      | - 20 meq tablet          | - Possibly contains gluten   |
| - Rabeprazole (Eisai)                                    | - 20 mg tablet           | - Possibly contains gluten   |
| - Ritonavir (AbbVie)                                     | - 100 mg tablet          | - Possibly contains gluten   |
| - Ritonavir (AbbVie)                                     | - 100 mg tablet          | - Possibly contains gluten   |
| - Ritonavir (AbbVie)                                     | - 80 mg/mL solution      | - Possibly contains gluten   |
| - Rivaroxaban (Janssen)                                  | - 10, 15, and 20 mg tablets | - Possibly contains gluten   |
| - Saquinavir (Genentech)                                 | - 200 and 500 mg capsules| - Possibly contains gluten   |
| - Sitagliptin (Merck)                                    | - 25, 50, and 100 mg tablets | - Possibly contains gluten   |
| - Sulfamethoxazole/trimethoprim DS (Amneal)              | - 800 mg/160 mg tablet   | - Possibly contains gluten   |
| - Telmisartan (BoehringerIngelheim)                     | - 20, 40, and 80 mg tablets | - Possibly contains gluten   |
| - Tramadol (Mylan)                                       | - 50 mg tablet           | - Possibly contains gluten   |
| - Triazolam (Greenstone)                                | - 0.125 and 0.25 mg tablets | - Possibly contains gluten   |
| - Valsartan (Novartis)                                   | - 40, 80, 160, and 320 mg tablets | - Possibly contains gluten   |
| - Vancomycin (Baxter)                                    | - 1 g injection          | - Possibly contains gluten   |
| - Nebivolol (Forest)                                     | - 2.5, 5, 10, and 20 mg tablets | - Contains gluten             |
| - Tramadol (Amneal)                                      | - 50 mg tablet           | - Contains gluten            |

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