

FOOD ALLERGENS SUBMITTED TO COMPULSORY FOOD LABELLING IN THE 50 HIGHEST-SELLING DRUGS IN FRANCE

D. Piney (1), N. Commun (1), G. Kanny (2)

SUMMARY: Many active ingredients and excipients present in allopathic drugs derive from food allergens normally associated with compulsory food labelling. This study was undertaken to evaluate the presence of these components in the various pharmaceutical formulations of the 50 highest-selling drugs in French pharmacies in 2002 (in quantity and/or value), and to assess their labelling on the packaging of these drugs. The 174 pharmaceutical formulations of 86 drugs were studied and the composition of each one was identified using data-processing software. An excipient deriving from an allergen with obligatory labelling in food is present in 58.6% of the studied pharmaceutical formulations. Almost one third (32.2%) of these medications are correctly labelled since the excipients in question are already known to have adverse effects. This study demonstrates the actual presence of components derived from allergens with compulsory food labelling in the 50 highest-selling pharmaceutical products in France (in value and/or volume). Given the absence of clear labelling of food allergens in drugs, allergologists must inform both the medical and public communities of this potential risk. It is equally important that the pharmaceutical laboratories implement clear, informative labelling of food allergens, similar to that of the food industry.

Many active ingredients and excipients present in allopathic drugs derive from food allergens normally associated with compulsory labelling (1), without being clearly labelled on the drug packaging. According to the European Directive 2003/89/EC dated November 10, 2003, the 12 families of food allergens requiring mandatory labelling on foods are:

- Gluten-containing cereals (i.e. wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and derived products
- Crustaceans and derived products
- Eggs and derived products
- Fish and derived products
- Peanuts and derived products
- Soybeans and derived products
- Milk and derived products (including lactose)
- Nuts: i.e. Almond (*Amygdalus communis* L.), Hazelnut (*Corylus avellana*), Walnut (*Juglans regia*), Cashew (*Anacardium occidentale*), Pecan nut (*Carya illinoensis* (Wangenh.) K. Koch), Brazil nut (*Bertholletia excelsa*), Pistachio nut (*Pistacia vera*), Macadamia nut and Queensland nut (*Macadamia ternifolia*) and derived products

(1) Pharmacie ; (2) Médecine Interne, Immunologie Clinique et Allergologie, Centre Hospitalier de Nancy, Hôpital Central, 29 avenue du Maréchal de Lattre de Tassigny - 54035 Nancy

- Celery and derived products
- Mustard and derived products
- Sesame seeds and derived products
- Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre expressed as SO₂.

We evaluated the presence of components derived from food allergens requiring obligatory labelling (FAROL) in various pharmaceutical forms of the 50 highest-selling drugs in French pharmacies in 2002 (in quantity and/or value) (2). Sulphites were not taken into account because they belong to excipients known to have a recognized action or effect and consequently are clearly labelled on the drug. The excipients known to have a recognized action or effect are those whose presence may require precautions for use in certain categories of patients and are published by the French Agency for the Sanitary Safety of Health Products (AFSSAPS) in the appendix to the list of generic drugs regularly updated in decisions published in the French government gazette (*Journal Officiel*).

MATERIAL AND METHODS

The 50 highest-selling drugs in French pharmacies in 2002 (table I) in value and/or quantity were first po-

led and then classified in order to eliminate those present in the two lists published by the AFSSAPS (2).

The various pharmaceutical formulations of these drugs were processed separately. The composition of each drug was then studied using the Thériaque data base (3), consulted in July 2004, and the Vidal 2003 (4) and 2004 (5) drug compendiums which contain the Summaries of Product Characteristics (SPC). The active ingredients and excipients, deriving or possibly deriving from FAROL were indexed.

The drugs possibly containing a FAROL were counted and classified into four categories:

- *Allergen labelled because the excipient is known to have a recognized action or effect:* the FAROL is identifiable because it concerns an excipient known to have a recognized action or effect and is thus labelled on the external packaging of the drug;
- *Allergen not labelled:* the FAROL is not labelled on external packaging because it is not considered to be an excipient known to have a recognized action or effect;
- Possible allergen in flavoring;
- Non identifiable allergen: for example lecithin without specified origin.

We identified the presence of flavoring in the targeted drugs and assessed the composition. We found:

- drugs with at least one flavor;
- flavor of unknown composition;
- drugs with a flavor possibly derived from a FAROL.

RESULTS

Our research highlighted some differences between the Thériaque data base and the Vidal drug compendiums (4, 5). Thériaque highlighted an additional excipient of probable allergenic origin on three occasions, probably because it has been updated more recently and has multiple sources of information: SPC from the AFSSAPS, European Public Assessment Reports (EPAR) from the European Agency for the Evaluation of Medicinal Products (EMA), Merck Index, Nominum Index, etc. Our analysis uses the data extracted from Thériaque (table 1).

The 50 highest-selling drugs in France in 2002 (in value and/or volume) consist in 86 drugs and 174 pharmaceutical formulations. Among these 174 pharmaceutical formulations, 58.6% contain at least one excipient derived from a FAROL. 32.2% contain only excipients known to have a recognized action or effect and the identification of the FAROL is possible. 26.4% of the drugs contain excipients deriving or possibly deriving from a FAROL without labelling (table 2).

Various examples were found:

- the excipient or the active ingredient is or clearly derives from a known FAROL (1.1% of the medicinal specialities), for example: lysozyme, condensed milk;
- the excipient may derive from a FAROL but lack of information prevents us from knowing the exact origin (6.9% of the specialities), for example: sodium carboxymethyl starch, lecithin;
- the random labelling of flavoring gives rise to a singular situation: the composition is not indicated in 18.4% of the specialities.

Out of 35 specialities containing flavoring (Table 3), the Thériaque database provided details for 22 of them (3). Twelve contained a flavor base which could possibly derive from a FAROL (lactose or maltodextrin).

We compared the number of drugs whose flavor was mentioned in Vidal 2001 (7) with the results of our study. For 21 existing drugs in 2001 and for which the composition of the flavor is currently known, only 3 were detailed in Vidal 2001. For one of these drugs, the name of the flavor base (maltodextrin) is modified to dextrin without modification of the component.

DISCUSSION

This analysis demonstrates the presence of FAROL in the 50 highest-selling drugs (in value and/or volume) in France in 2002. If the FAROL is classified as an excipient known to have a recognized action or effect, labelling is compulsory on the external packaging of the drug. Other excipients not found in this list need not be labelled.

Some excipients are labelled with the names of categories (lecithins, starches, flavors, etc.) with no precise information on its exact nature and origin. The labelling of the excipient or the active ingredient may not indicate the exact origin of the product clearly enough for unsuspecting allergic patients: in the absence of clear, informative labelling, it is necessary to teach patients how to decipher labels correctly. A patient allergic to egg must be informed that the lysozyme in LYSOPAINE® contains an egg protein, or that the malt in LAXAMALT® comes from barley (source of gluten). Clearer and more informative labelling would reduce the risk of error when reading labels. These excipients and active ingredients derived from FAROL may be hidden allergens for allergic patients. The absence of clear labelling requires allergologists to implement a strategy of assistance in reading and deciphering labels and the names of various products derived from the FAROL (8). It is similarly necessary to

1 - In value			2 - In quantities		
Row 2002 (row 2001)	Product	Classify	Row 2002 (row 2001)	Product	Classify
1 (1)	MOPRAL® omeprazole	Anti-ulcer	1 (2)	DOLIPRANE® paracetamol	Analgesics
2 (2)	TAHOR® atorvastatin	Lipid-lowering	2 (1)	EFFERALGAN® paracetamol	Analgesics
3 (54)	PLAVIX® clopidogrel	Platelet aggregation inhibitor	3 (3)	DAFALGAN® paracetamol	Analgesics
4 (7)	SERETIDE® fluticasone / salmeterol	Anti-asthmatic	4 (4)	DI-ANTALVIC® dextropropoxifen / paracetamol	Analgesics
5 (5)	ELISOR® pravastatin	Lipid-lowering drug	5 (5)	SPASFON® phloroglucinol	Anti-spasmodic
6 (6)	ZOCOR® simvastatin	Lipid-lowering drug	6 (6)	STILNOX® zolpidem	Hypnotic
7 (10)	VASTEN® pravastatin	Lipid-lowering drug	7 (8)	KARDEGIC® lysine acetyl salicylate	Platelet aggregation inhibitor
8 (9)	DEROXAT® paroxetine	Antidepressant	8 (9)	LEVOTHYROX® levothyroxine	Hormones
9 (58)	VIOXX® rofecoxib	Anti-arthritis	9 (7)	ASPEGIC® lysine acetyl salicylate	Analgesics
10 (13)	AMLOR® amlodipine	Anti-hypertension	10 (10)	PROPOFAN® cafein / dextropropoxifen / paracetamol	Analgesics
11 (11)	DOLIPRANE® paracetamol	Analgesics	11 (11)	DAFLON® flavonoid of rutace	Venotonic
12 (12)	EFFERALGAN® paracetamol	Analgesics	12 (34)	ADVIL® ibuprofen	Anti-inflammatory
13 (4)	CELEBREX® celecoxib	Anti-arthritis	13 (13)	MOPRAL® omeprazol	Anti-ulcer
14 (21)	OGAST® lansoprazole	Anti-Ulcer	14 (12)	MAGNE B6® magnesium / pyridoxin	Metabolism
15 (8)	PROZAC® fluoxetine	Antidepressant	15 (20)	DEROXAT® paroxetin	Antidepressant
16 (19)	ORELOX® cefpodoxime	Antibiotic	16 (14)	ZYRTEC® cetirizine	Anti-histaminic
17 (29)	TRIA TEC® ramipril	Anti-hypertension	17 (22)	ELUDRIL® chlorhexidin / chlorobutanol	E.N.T. – Anti-bacterial
18 (21)	LOVENOX® enoxaparin	Anticoagulant	18 (23)	VOLTARENE® diclofenac	Anti-inflammatory
19 (16)	TANAKAN® ginkgo biloba	Vasodilator	19 (24)	MOTILIUM® domperidon	Anti-emetic
20 (28)	LANZOR® lansoprazole	Anti-ulcer	19 (13)	RENUTRYL®	Nutrition
21 (23)	SEROPRAM® citalopram	Antidepressant	20 (30)	TAHOR® atorvastatin	Lipid-lowering drug
22 (13)	VASTAREL® trimetazidine	Anti-ischaemic	21 (35)	TEMESTA® lorazepam	Anxiolytic
23 (33)	ARICEPT® donepezil	Alzheimer's disease	22 (37)	ENDOTELON® Procyanidolic Oligomers	Venotonic
24 (20)	PYSOTACINE® pristinamycin	Antibiotic	23 (29)	GAVISCON® alginate acid / aluminium hydroxide	Anti-acid
25 (22)	SUBUTEX® buprenorphine	Substitute treatment	24 (33)	GINKOR® ginkgo biloba / heptaminol / troxerutine	Venotonic
26 (24)	LIPANTHYL® fenofibrate	Lipid-lowering drug	25 (28)	LEXOMIL® bromazepam	Anxiolytic
27 (31)	APROVEL® irbesartan	Anti-hypertension	26 (47)	GLUCOPHAGE® metformin	Anti-diabetic
28 (25)	DAFLON® flavonoid of rutace	Venotonic	27 (22)	IMOVANE® zopiclone	Hypnotic
29 (27)	PARIET® rabeprazole	Anti-ulcer	28 (27)	CLARITYNE® loratadine	Anti-histaminic
30 (30)	XALATAN® latanoprost	Glaucoma treatment	29 (50)	BRONCHOKOD® carbocisteine	Cough preparation
31 (26)	ZYRTEC® cetirizine	Anti-histaminic	30 (21)	VASTAREL® trimetazidine	Anti-ischaemic
32 (313)	COVERSYL® perindopril	Anti-hypertension	31 (40)	PIASCLEDINE® avocado / soya	Anti-rheumatic
33 (39)	AVONEX® interferon beta 1A	Multiple sclerosis treatment	32 (43)	LAMALINE® cafein / opium / paracetamol	Analgesics
34 (282)	SYMBICORT® budesonide / formoterol	Anti-asthmatic	33 (25)	FONZYLANE® buflomedil	Vasodilator
35 (30)	PULMICORT® budesonide	Anti-asthmatic	34 (31)	XANAX® alprazolam	Anxiolytic
36 (40)	REBETOL® ribavirin	Treatment of hepatitis C	35 (55)	ORELOX® cefpodoxime	Antibiotic
37 (53)	ART 50® diacerein	Anti-arthritis	36 (16)	CLAMOXYL® amoxicillin	Antibiotic
38 (64)	RISPERDAL® risperidone	Antipsychotic	37 (34)	LASILIX® furosemide	Diuretic
39 (37)	COZAAR® losartan	Anti-hypertension	38 (41)	PIVALONE® tixocortol	E.N.T.
40 (15)	AUGMENTIN® amoxicillin / clavulanate potassium	Antibiotic	39 (36)	DUPHASTON® dydrogesterone	Progestational
41 (45)	TOPALGIC® tramadol	Analgesics	40 (56)	FORLAX® macrogol 4000	Laxative
42 (55)	ZELITREX® valaciclovir	Antiviral systemic	41 (48)	NUROFEN® ibuprofen	Analgesics
43 (43)	DEPAKINE® valproate sodium	Anti-epileptic	42 (39)	LYSOPAIN® bacitracin / lysozyme / papain	E.N.T.
44 (59)	LAMISIL® terbinafine	Antifungal	43 (46)	DIPROSEPT® betamethasone / clioquinol	Disinfectant
45 (34)	FORADIL® formoterol	Anti-asthmatic	44 (44)	DIALGIREX® dextropropoxifen / paracetamol	Analgesics
46 (44)	LODALES® simvastatin	Lipid-lowering	45 (18)	AUGMENTIN® amoxicillin / clavulanate potassium	Antibiotic
47 (54)	HYPERIUM® rilmenidine	Anti-hypertension	46 (42)	KETUM® ketoprofen	Anti-inflammatory
48 (79)	TAREG® valsartan	Anti-hypertension	48 (38)	VEINAMITOL® troxerutine	Venotonic
49 (-)	INEXIUM® esomeprazole	Anti-ulcer	49 (44)	TANAKAN® ginkgo biloba	Vasodilator
50 (72)	SOLIAN® amisulpride	Antipsychotic	50 (26)	PROZAC® fluoxetine	Antidepressant

Table 1.

train pharmacists to avoid using food allergens for allergic patients.

Labelling of components of flavors added to mask or improve the taste and smell of certain drugs is random. The composition of the flavors is complex: various solvents, bases, dyes, preservatives and additives. They are classified as follows (6):

- chemically defined flavoring agents (i.e.: levomenthol extracts from *Mentha arvensis*),
- artificial flavoring agents, not existing in a natural state (i.e.: menthol, vanillin),
- complex flavoring agents manufactured from natural products
- flavor transformation agents obtained by heating substances that are not necessarily flavoring agents.

The term "flavor" can refer to a combination of these various categories. Our research shows the benefit to be gained if pharmaceutical laboratories published the precise composition of the flavours used in their medicinal products.

The presence of lactose or wheat-derived products is common in flavors of known composition. It is important that pharmaceutical laboratories implement clearly informative labelling for allergic patients by indicating the name of the FAROL: milk, wheat, etc.

Pharmacists have an important role to play when replacing standard drugs by generics. They must know the exact composition of the drugs they intend to replace when dealing with patients with a known

	Number of drugs	Number of drugs without FAROL	Number of drugs possibly containing at least a FAROL	Identifiable FAROL because excipient known to have a recognized action or effect	FAROL not labelled	Possible FAROL in the form of flavoring	Possible FAROL but not shown
Tablets / Capsules	100	33	67	50	1	5	11
Sachets	13	2	11			11	
Oral suspensions / Syrups	25	7	18	1	1	15	1
Injectable	15	13	2	2			
Aerosols / throat sprays	8	4	4	3		1	
Topical route / mouth wash	6	6					
Eyedrops	2	2					
Suppositories	5	5					
Total	174	72	102	56	2	32	12
Ratio (%)		41.4	58.6	32.2	1.1	18.4	6.9

Table 2: Food allergens submitted to compulsory labelling in the 50 highest-selling drugs (in value and/or volume) in France in 2002.

	Drugs containing a flavor	Flavors whose composition is published (4, 6)	Presence of a potential allergen in flavor
Tablets / Capsules	7	4	4
Sachets	11	8	6
Oral suspensions / Syrups	16	10	2
Injectable			
Aerosols / throat sprays	1		
Topical route / mouth wash			
Eyedrops			
Suppositories			
Total	35	22	12

Table 3: Flavors present in the various pharmaceutical formulations of the 50 highest-selling drugs (in value and/or volume) in France in 2002.

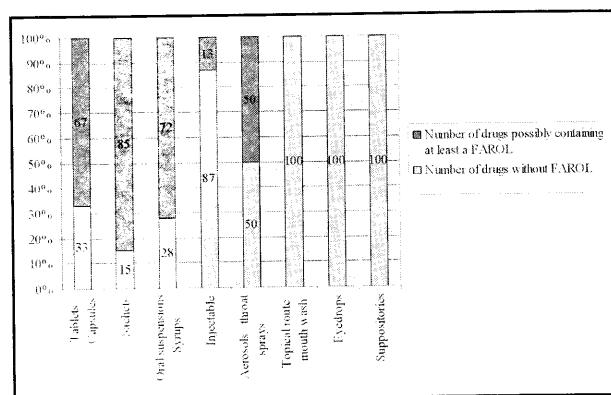


Figure 1: FAROL present in the various pharmaceutical formulations of the 50 highest-selling drugs (in value and/or volume) in France in 2002.

allergy. In addition to these measures, it is necessary to follow the European Directive on the compulsory labelling of certain allergens in food, and to take into account the risk of food allergy in pharmacy and legislate for clear labelling of FAROL in drugs.

References

1. The European Parliament. Directive 2003/89/EC amending directive 2000/11/EC as regards indication of the ingredients present in foodstuffs. Official Journal of the European Union November 27, 2003: L 2003, 308,15-18.
2. AFSSAPS, Direction de l'Evaluation de la Publicité et des Produits Cosmétiques et Biocides. (juillet, 2004). Les cinquante produits les plus vendus en officine en 2002, [en ligne],16. <http://trouveur.chu-rouen.fr/pharmacologie/crpv/pdf/med2004.pdf>.
3. Groupement d'Intérêt Economique - Système d'Information sur les Produits de Santé. (pages consultées le 12 juillet 2004). Banque de données sur le médicament Thériaque., [en ligne]. www.theriaque.org.
4. Vidal. Vidal 2003. Issy Moulineaux: Vidal; 2003.
5. Vidal. Vidal 2004. Issy Moulineaux: Vidal; 2004.
6. Le Hir A. Pharmacie galénique. Bonnes pratiques de fabrication des médicaments. 8 ed. Paris: Masson; 2001.
7. Vidal. Vidal 2001. Issy Moulineaux: Vidal; 2001.
8. Moneret-Vautrin DA, Kanny G. Masked and labelled food allergens. *Allerg Immunol* 1998;30:38-40.

