## Table A: Summary of FDA and European Commission Guidance for Industry for Adverse Drug Reaction reporting in product information documents

## Food and Drug Administration. Guidance for Industry

### Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

**INTRODUCTION**

Applicants should assess such factors as seriousness, severity, frequency, and strength of causal association in determining which adverse reactions to include

**ADVERSE REACTIONS section**

In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients

Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided

Separate lists are required for:

adverse reactions identified from clinical trials

spontaneous reports after a drug has been marketed

**A. Making the Most Clinically Important Information Accessible**

The ADVERSE REACTIONS section should make it easier for health care practitioners to recognize and retain the adverse reactions information that is most important to prescribing decisions

The beginning of the ADVERSE REACTIONS section should identify the most clinically significant adverse reactions

**B. Adverse Reactions From Clinical Trials**

1. Description of Data Sources

The presentation of adverse reactions information identified from clinical trials must be preceded by information necessary to interpret the adverse reactions

e.g. number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials

2. Statement on the Significance of Adverse Reaction Data Obtained From Clinical Trials

3. Presentation of Common Adverse Reactions (the Adverse Reactions Table)

List the adverse reactions identified from clinical trials that occurred at or above a specified rate appropriate to the database

The listing must include the rate of occurrence of an adverse reaction for the drug and any comparators

a. Use Best Available Data e.g. placebo-controlled

b. Description of Data Sources for the Table, includes:

the basis for including adverse reactions in the table (e.g., all ARs occurring at > n% in the treated group and for which the rate for drug exceeds the rate for placebo)

the way in which adverse reaction rates were derived e.g. was the rate derived from all reported adverse events of that type not present at baseline or from a subset of reported events deemed by investigators to be drug-related

indicate the types of studies from which the information in the table was derived and whether the study data were pooled

c. How Many Tables?

A single adverse reaction table will usually be adequate

However, it may be more informative to present data in more than one table when a drug's adverse reaction profile differs substantially from one setting or population to another

4. Presentation of Less Common Adverse Reactions

Inclusion of less common adverse reactions, but for which there is some basis to believe there is a causal relationship between the drug and the event

Lengthy lists of adverse events unlikely to have been caused by the drug are of little or no value to prescribers, and are therefore inappropriate for inclusion in labeling
Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event

Typical reasons to suspect causality include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected (4) occurrence of an event typical of drug-induced adverse reactions e.g. liver necrosis.

Non-serious, low-frequency adverse events should be listed only when there is strong evidence that the drug caused the event. Such evidence may include, for example, positive challenge/dechallenge tests or rate of occurrence in a large controlled trial that, although low, is markedly imbalanced between drug and control arms.

5. Commentary on Listings of Common and Less Common Adverse Reactions

For adverse reactions with significant clinical implications must be supplemented with additional details about the nature, frequency, severity, dose-response, and demographic characteristics of the adverse reaction, to the extent data are available and important

a. Information on Nature, Frequency, and Severity

b. Dose-Response Information

c. Demographic and Other Subgroups

d. Multiple Indications

e. Multiple Formulations

**C. Presentation of Adverse Reaction Information From Spontaneous Reports**

The ADVERSE REACTIONS section must list adverse reactions identified from domestic and foreign spontaneous reports

This listing must be separate from the listing of adverse reactions identified in clinical trials

and must also be preceded by information necessary to interpret the adverse reactions

Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug

NB: full guidance listed in reference below. This summary has been constructed with relevance to the research objectives in this study.

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075057.pdf

## European Commission. A guideline on summary of product characteristics (SmPC)

**INTRODUCTION**

The use of MedDRA as described in the annex for section 4.8 should be applied though the SmPC, in particular for sections 4.3 and 4.4 and 4.8

**4.8 Undesirable effects**

This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility

Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC

It is important that the whole section is worded in concise and specific language

**a. Summary of the safety profile**

Provide information about the most serious and/or most frequently occurring adverse reactions

If known, it may be helpful to indicate the timing when adverse reactions occur

Inform about adverse reactions associated with long-term use

Frequencies of cited adverse reactions should be stated as accurately as possible

**b. Tabulated list of adverse reactions**

A single table (or structured listing) should list all adverse reactions with their respective frequency category

Separate tables are acceptable in exceptional cases where the adverse reaction profiles markedly differ depending on the use of the product

The table should be introduced stating the source of the safety database (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting

The table should be presented according to the MedDRA system organ classification

Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology (usually Preferred Term (PT) level)

Within each system organ class, the adverse reactions should be ranked under headings of frequency, most frequent reactions first.

Within each frequency grouping, adverse reactions should be presented in the order of decreasing seriousness.

Use Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

**c. Description of selected adverse reactions**

Include information characterising specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction

Information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases

The information should provide frequency and may describe for example reversibility, time of onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose relationship, relationship with duration of exposure or risk factors

**d. Paediatric population**

The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data)

Uncertainties due to limited experience should be stated

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations

**e. Other special populations**

Include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype

**Further guidance on the estimation of frequency of adverse reactions**

If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied and thus resulted in an estimate of clearly higher validity

Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect

**Adverse reactions from clinical trials**

The frequency of adverse reactions should be derived from pooled placebo-controlled studies if these data are available

When a common, very common or serious adverse reaction (e.g. suicide) also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective

**Adverse reactions from spontaneous reporting**

In case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category
If the adverse reaction has never been observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies

---

NB: full guidance listed in reference below. This summary has been constructed with relevance to the research objectives in this study.

http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

**Online supplementary material**

## Table B: Availability of product information documentation for anticonvulsants and antidepressants included into the study.[a]

| Anticonvulsants | Brand name | Europe | USA | Included |
|---|---|---|---|---|
| Carbamazepine | Tegretol | yes | yes | yes |
| Gabapentin | Neurontin | yes | yes | yes |
| Lamotrigine | Lamictal | yes | yes | yes |
| Oxcarbazepine | Trileptal | yes | yes | yes |
| Phenytoin | Epanutin/Dilantin | yes | yes | yes |
| Pregabablin | Lyrica | yes | yes | yes |
| Sodium Valproate | Epilim | yes | no | no |
| Topiramate | Topamax | yes | yes | yes |
| Zonisamide | Zonegran | yes | yes | yes |
| **Antidepressants** | **Brand name** | **Europe** | **USA** | **Included** |
| Amitriptyline | Elavil | yes | no | no |
| Citalopram | Cipramil | yes | no | no |
| Clomipramine | Anafranil | yes | yes | yes |
| Desipramine | Norpramin | no | yes | no |
| Duloxetine | Cymbalta | yes | yes | yes |
| Fluoxetine | Prozac | yes | yes | yes |
| Imipramine | Janimine | no | yes | no |
| Mianserin | Mianserin | yes | no | no |
| Nortriptyline | Allegron | yes | no | no |
| Venlafaxine | Effexor/Efexor | yes | yes | yes |

[a] drugs included where those identified from a systematic review of randomised controlled trials evaluating treatments for post-herpetic neuralgia (PHN) or painful diabetic neuropathy (PDN)

## Table C: Data reported by document grouped by drug

| | Drug | Carbamazepine n(%) | | Gabapentin n(%) | | Lamotrigine n(%) | | Oxcarbazepine n(%) | | Pregabablin n(%) | | Topiramate n(%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | European | USA | SmPC | USPI | SmPC | USPI | SmPC | USPI | SmPC | USPI | SmPC | USPI |
| Adverse Reactions | n | 164 | 122 | 117 | 425 | 56 | 241 | 89 | 215 | 179 | 275 | 265 | 248 |
| Data source of AR report | 1) Clinical trial | 2 (1) | 2 (2) | 88 (75) | 412 (99) | 55 (98) | 224 (93) | 79 (89) | 201 (93) | 158 (88) | 267 (97) | 256 (97) | 244 (98) |
| | 2) Spontaneous report/other | 2 (1) | 0 (0) | 28 (24) | 13 (3) | 0 (0) | 11 (5) | 10 (11) | 14 (7) | 21 (12) | 8 (3) | 7 (3) | 1 (<1) |
| | 3) Unspecified | 160 (98) | 120 (98) | 1 (1) | 0 (0) | 1 (2) | 6 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (1) | 3 (1) |
| For each AR identified from a clinical trial is there information on: | 1) No. of participants | 0(0) | 2 (100) | 0 (0) | 412(100) | 0 (0) | 221 (99) | 0 (0) | 71 (35) | 158 (100) | 265 (99) | 256 (100) | 241 (98) |
| | 2) Risk estimates | 0(0) | 2 (100) | 86 (98) | 330 (80) | 0 (0) | 221 (99) | 71 (80) | 71 (35) | 158 (100) | 265 (99) | 256 (100) | 226 (92) |
| | 3) Risk estimates by severity | 0(0) | 2 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | 4) length of study | 0 (0) | 2 (100) | 0 (0) | 3 (<1) | 0 (0) | 1 (<1) | 0 (0) | 0 (0) | 0 (0) | 265 (99) | 0 (0) | 1 (<1) |
| Is there any information on AR risk by: | 1) Indication | no | yes | no | yes | yes | yes | no | yes | no | yes | no | yes |
| | 2) Dose | no | no | no | no | no | yes | no | yes | no | yes | no | yes |
| Did the document contain any information on: | 1) Recurrent ARs | no | no | no | no | no | no | no | no | no | no | no | no |
| | 2) Duration of AR | no | no | no | no | no | no | no | no | no | no | no | no |
| | **Drug** | **Zonisamide** | | **Clomipramine** | | **Duloxetine** | | **Fluoxetine** | | **Epanutin** | | **Efexor** | |
| | | SmPC | USPI | SmPC | USPI | SmPC | USPI | SmPC | USPI | SmPC | USPI | SmPC | USPI |
| Adverse Reactions | n | 97 | 186 | 96 | 325 | 136 | 142 | 111 | 95 | 86 | 65 | 126 | 105 |
| Data source of AR report | 1) Clinical trial | 0 (0) | 143 (77) | 1 (1) | 319 (98) | 0 (0) | 107 (76) | 1 (1) | 79 (83) | 0 (0) | 2(3) | 3 (2) | 36 (34) |
| | 2) Spontaneous report/other | 0 (0) | 8 (4) | 5 (5) | 5 (2) | 2 (1) | 23 (16) | 3 (3) | 2 (2) | 0 (0) | 0 (0) | 6 (5) | 34 (32) |
| | 3) Unspecified | 97 (100) | 35 (19) | 90 (94) | 1 (<1) | 134 (98) | 11 (8) | 107 (96) | 14 (15) | 86 (100) | 63 (97) | 117 (93) | 35 (33) |
| For each AR identified from a clincal trial is there information on: | 1) No. of participants | - | 143 (100) | 0 (0) | 298 (93) | - | 107 (100) | 0(0) | 35(44) | - | 0(0) | 0(0) | 25 (69) |
| | 2) Risk estimates | - | 140 (98) | 0 (0) | 299 (93) | - | 99 (93) | 0(0) | 79 (100) | - | 0(0) | 1 (33) | 25 (69) |
| | 3) Risk estimates by severity | - | 3 (2) | 0 (0) | 1 (<1) | - | 8 (7) | 0(0) | 79 (100) | - | 0(0) | 0(0) | 0 (0) |
| | 4) length of study | - | 2 (1) | 0 (0) | 0 (0) | - | 84 (79) | 0 (0) | 1 (100) | - | 0 (0) | 1 (33) | 0 (0) |
| Is there any information on AR risk by: | 1) Indication | no | yes | no | no | yes | yes | no | yes | no | no | no | no |
| | 2) Dose | no | no | no | no | no | no | no | no | no | no | no | no |
| Did the document contain any information on: | 1) Recurrent ARs | no | no | no | no | no | no | no | no | no | no | no | no |
| | 2) Duration of AR | no | no | no | no | no | no | no | no | no | yes | no | no |

**Table D: Dictionaries used to code adverse event terms by origin of document**

| | Dictionary used: matched pair | |
|---|---|---|
| **Drug** | **Europe** | **USA** |
| Carbamazepine | not reported | WHO-ART |
| Gabapentin | not reported | not reported |
| Lamotrigine | not reported | COSTART |
| Oxcarbazepine | not reported | not reported |
| Pregabablin | not reported | COSTART |
| Topiramate | not reported | COSTART |
| Zonisamide | MedDRA | not reported |
| Clomipramine | MedDRA | not reported |
| Duloxetine | MedDRA | COSTART |
| Fluoxetine | not reported | not reported |
| Epanutin | not reported | not reported |
| Efexor | not reported | WHO-ART & investigators terminology |