university of groningen

University Medical Center Groningen

University of Groningen

# Quality of drug label information on QT interval prolongation

Warnier, Miriam J.; Holtkamp, Frank A.; Rutten, Frans H.; Hoes, Arno W.; De Boer, Anthonius; Mol, Peter G.M.; De Bruin, Marie L.

*Published in:*
International Journal of Risk and Safety in Medicine

*DOI:*
10.3233/JRS-140612

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*
Publisher's PDF, also known as Version of record

*Publication date:*
2014

Link to publication in University of Groningen/UMCG research database

*Citation for published version (APA):*
Warnier, M. J., Holtkamp, F. A., Rutten, F. H., Hoes, A. W., De Boer, A., Mol, P. G. M., & De Bruin, M. L. (2014). Quality of drug label information on QT interval prolongation. *International Journal of Risk and Safety in Medicine*, *26*(2), 89-98. https://doi.org/10.3233/JRS-140612

**Copyright**
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

**Take-down policy**
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

Download date: 30-04-2023

International Journal of Risk & Safety in Medicine 26 (2014) 89–98
DOI 10.3233/JRS-140612
IOS Press


Medical Law

# Quality of drug label information on QT interval prolongation

Miriam J. Warnier[a,b], Frank A. Holtkamp[c,d], Frans H. Rutten[b], Arno W. Hoes[b], Anthonius de Boer[a], Peter G.M. Mol[c,d] and Marie L. De Bruin[a,c,*]

[a]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands*
[b]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*
[c]*Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands*
[d]*Department of Clinical Pharmacology, University Medical Center Groningen, Groningen, The Netherlands*

Received 12 December 2013
Accepted 24 March 2014

**Abstract.**
**BACKGROUND:** Information regarding QT-prolongation in the drug label may vary between products. This could lead to suboptimal risk minimization strategies.
**OBJECTIVE:** To systematically assess the variation in the extent and content of information on QT prolongation in the summary of product characteristics (SPC) of recently approved medicinal products.
**METHODS:** Drug labels of products centrally approved in Europe between 2006 and 2012 were screened. Of drugs including the term 'QT' in the SPC, the message on QT-prolongation ('no prolongation'/'unclear drug-QT association'/'possibly QT-prolongation'/'QT-prolongation') and the advice on cautionary measures pertaining to QT-prolongation in the label were examined, as well as their association.
**RESULTS:** Of the 175 screened products, 44 contained information on QT in the SPC ('no QT-prolongation': 23%, 'unclear drug-QT association': 43%, 'possibly QT-prolongation': 16%, 'QT-prolongation': 18%). 62% contained advices to act with caution in patients with additional risk factors for QT-prolongation. Products that more likely to have QT-prolonging properties according to the SPC provided more information on QT-prolongation in the SPC ('no prolongation': 10% and for the category 'QT-prolongation': 100%).
**CONCLUSIONS:** The extent and content of information on QT-prolongation varies considerably between SPCs, and in almost half of the drugs a clear message on QT-prolongation was lacking in the SPC.

Keywords: Cardiovascular agents/adverse effects, drug approval, torsades de pointes/chemically induced, drug labeling/legislation & jurisprudence, communication

*Address for correspondence: Marie L. De Bruin, PharmD, PhD, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, PO-box 80082, 3508 TB, Utrecht, The Netherlands. Tel.: +31 30 253 7324; Fax: +31 30 253 9166; E-mail: m.l.debruin@uu.nl.

0924-6479/14/$27.50 © 2014 – IOS Press and the authors. All rights reserved

## 1. Introduction

Prolongation of cardiac repolarization, manifested as a prolonged QT interval on the surface electrocardiogram (ECG) may predispose to fatal ventricular arrhythmias such as torsade de pointes, ventricular tachycardia or fibrillation, and sudden cardiac death [1, 2]. At present, cardiac arrhythmia associated with QT interval prolongation is one of the most common adverse drug reactions leading to regulatory action, including withdrawal of a drug from the market [3, 4]. Although the occurrence of QT interval prolongation is generally rare, it can be potentially fatal [1, 2]. As a result, the regulatory authorities have strengthened the requirements for premarketing testing of pro-arrhythmic effects of new drugs (so called 'thorough QT studies' that evaluate the effect of the drug on cardiac repolarization), over the last decade. In 2005, the Food and Drug Administration (FDA), the European Medicine Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA) adopted the ICH E14 guideline, which recommends to perform a 'thorough-QT study' for all new drugs, as a basis to conclude on a compounds ability to cause QT prolongation [5, 6].

In case of any suspicion of QT prolongation before, but also after marketing authorization of a drug, information about this is commonly mentioned in specific sections of the drug labelling, also called the summary of product characteristics (SPC). The SPC is a legal document that sets out the conditions under which a certain medicinal product can be used safely and effectively [7, 8]. It contains a description of the products (chemical, pharmacological and pharmaceutical) properties as well as information on the clinical use including sections on e.g. contraindications, special warnings and precautions, interactions and undesirable effects. The SPC forms the basis of information for health professionals on how to use the specific product safely and effectively [7].

It has been noticed, however, that the quality of information on QT prolongation varies between products. This could hamper the usefulness of this information for health care providers and lead to suboptimal risk minimization strategies. Therefore, the aim of this study was to systematically assess the variation in the extent and content of information on QT prolongation in the SPC, in relation to the QT prolonging effects described in the SPC.

## 2. Methods

### *2.1. Study design and data collection*

A descriptive study was performed. Medicinal products centrally approved in the European Union (EU) between 1.1.2006 and 1.6.2012 were included. Duplicates, generics, fixed-dose combinations, and vaccines were excluded. The SPCs of the included products were identified from the European Medicines Agency (EMA) database of European public assessment reports [9] and screened to determine if the product included the word 'QT' in the SPC.

### *2.2. Characteristics of the selected products*

The following characteristics of the included products were recorded: indication (cardiovascular, endocrinology and metabolic, infectious disease, musculoskeletal and nervous system, oncology, immunology or 'other'), year of registration, and orphan drug status (yes/no). The size of the company of the marketing application holder was, in line with other studies, determined as small, medium-sized, or large, based on ranking by total revenue as reported in Script's Pharmaceutical Company League

Tables 2008. Companies were defined as large if ranked 1–20, medium-sized if ranked 21–150, and small if the company was not on the ranking list [10, 11].

### 2.3. Information on QT prolongation in the SPC

Of all products that mentioned 'QT' in the SPC, data on QT prolongation were extracted from the SPC. In order to evaluate the content of information on QT prolongation in the SPCs, the message on QT prolongation in the drug label was categorised into four subsets: 1. 'Drug does not prolong QT interval', 2. 'Unclear if the drug prolongs the QT interval', 3. 'Drug possibly prolongs QT interval', 4. 'Drug prolongs QT interval', based on the phrasing used to report on the degree of QT prolonging properties of the compound (Appendix 1). As we aimed on addressing the usefulness of drug labels for health care providers, we did not interpret the results of studies on QT prolongation reported in the label. MW and MDB independently categorised the drug labels of the included products into the four subsets. Consensus was used to resolve disagreement. If consensus could not be reached, discrepancies were resolved in discussion with PM.

In order to evaluate the extent of information on QT prolongation in the SPCs, we examined in which of the following sections of the SPC QT prolongation was mentioned: 4.3 contra-indications, 4.4 special warnings and precautions, 4.5 interactions, 4.8 undesirable effects, 4.9 overdose, 5.1 pharmacodynamics and 5.3 preclinical safety data. In addition, we determined whether the SPC provided information on the following three topics: 1. Advices to act with caution in patients with (additional) risk factors for QT prolongation, 2. An explanation for the association of QT prolongation with ventricular arrhythmia, torsade de pointes, and sudden cardiac arrest, and 3. Advices on monitoring of patients using the product. In addition we assessed whether the label contained information on thorough-QT studies.

Subsequently, the association between the content (message on QT prolongation in the drug label according to the four subcategories) and the extent (information on QT prolongation in the label according to three information topics mentioned above) was determined.

### 2.4. Data analysis

Values were presented as absolute numbers and proportions. All data were analysed using the statistical software package SPSS (SPSS for Windows, version 20.0, SPSS Inc.).

## 3. Results

### 3.1. Characteristics of the selected products

Of the 424 identified medicinal products, centrally approved in the EU between 1.1.2006 and 1.6.2012, we excluded 249 products (59%) for the following reasons: SPC duplicates ($n = 83$), generics ($n = 116$), fixed-dose combinations ($n = 27$), and vaccines ($n = 23$, Fig. 1). Of the remaining 175 products, one product that mentioned the word 'QT' in the SPC (rufinamide) was excluded as the warning was not on QT prolongation, but on QT shortening, and 44 (25%) of the SPCs mentioned QT prolongation (Appendix 2).

Characteristics of the 44 selected products are presented in Table 1. The most common indication was oncology ($n = 12$, 27%). Eighteen percent of the products was registered as orphan drugs. In the majority of the selected products a large company was involved ($n = 30$, 68%).

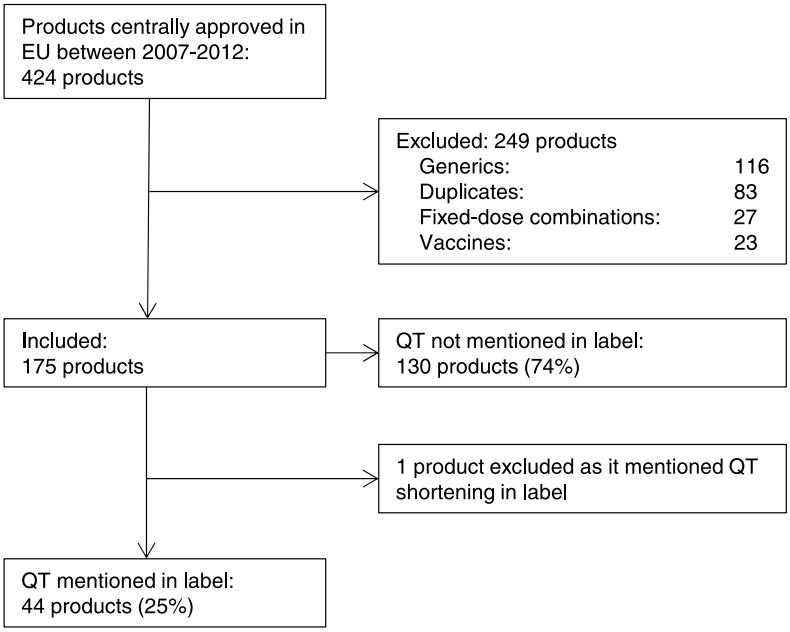


Fig. 1. Flow chart of inclusion of products.

### *3.2. Information on QT prolongation in the SPC*

In one-third of the 44 products, the main message on QT prolongation in the SPC was that either the drug prolongs the QT interval (18%), or that the drug *possibly* prolongs the QT interval (16%). In about a quarter of the products (23%) the SPC contained the message that the drug *does not* prolong the QT interval. For the remaining products (43%) no clear message on QT prolongation was included in the SPC (Table 2).

QT-related issues were most commonly reported in section 4.4 (special warnings and precautions, 66%) and section 4.8 (undesirable effects, 57%, Fig. 2). Concordantly, the products that either prolong or *possibly* prolong the QT interval according to the SPC most often reported QT related issues in section 4.4 (both 100%) and 4.8 (88% and 57%, respectively). In contrast, for products that mentioned 'no QT prolongation' in the SPC, QT prolongation was most often stated in section 5.1 (pharmacodynamics properties, 60%).

Sixty-two percent of the SPCs contained the advice to act with caution in patients with additional risk factors related to QT prolongation ($n = 25$, Table 2), and 16% of the SPCs explained the association of QT prolongation with ventricular arrhythmias ($n = 27$). The advice on monitoring of patients using the product was given in 34% of the SPCs ($n = 15$). The most frequently reported item was 'Use with caution concurrently with other drugs that prolong the QT-interval or anti-arrhythmics' ($n = 24$, 55%).

Products that were more likely to have QT prolonging properties according to the SPC provided more information on QT prolongation in the SPC. The proportion of products that provided information on at least one of the informative topics increased from 10% of the drugs that 'does not prolong the QT interval' according to the SPC to 100% of the drugs that either 'prolong' or 'possibly prolong' the QT (Table 2, Fig. 3). In contrast, the label of drugs that claimed to have 'no QT prolonging properties' in the label more often reported on thorough-QT studies (60%), than the labels of drugs that either 'prolong' (13%) or '*possibly* prolong' (14%) the QT interval according to the SPC.

Table 1
Characteristics of the included products ($n = 44$)

| Characteristics | QT mentioned in SPC $n = 44$ |
|---|---|
| Indication: | |
| Cardiovascular | 6 (14%) |
| Endocrinology and metabolic | 4 (9%) |
| Infectious disease | 6 (14%) |
| Musculoskeletal | 6 (14%) |
| and nervous system | |
| Oncology | 12 (27%) |
| Immunology | 3 (7%) |
| Others | 7 (16%) |
| Year of registration: | |
| 2006 | 3 (7%) |
| 2007 | 11 (25%) |
| 2008 | 5 (11%) |
| 2009 | 8 (18%) |
| 2010 | 5 (11%) |
| 2011 | 9 (21%) |
| 2012[a] | 3 (7%) |
| Orphan drug | 8 (18%) |
| Company size: | |
| Large | 30 (68%) |
| Medium | 10 (23%) |
| Small | 4 (9%) |

[a]Until 1.6.2012.

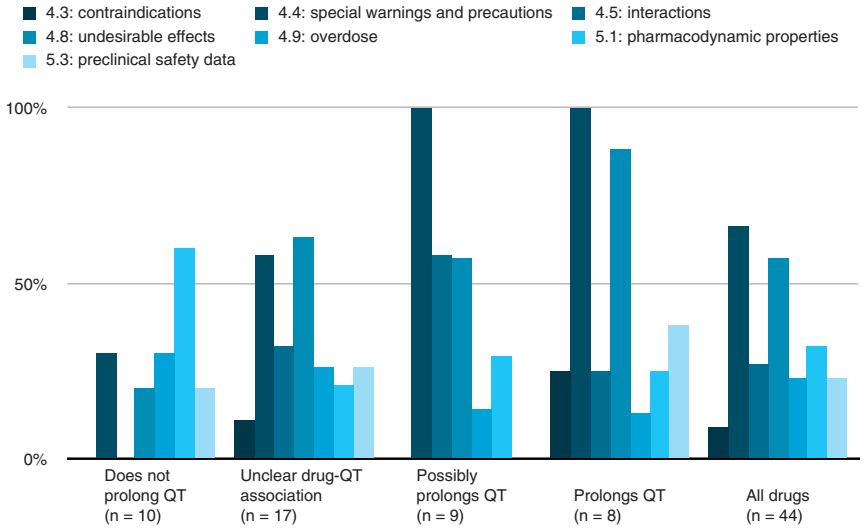


Fig. 2. Frequency of reporting on QT prolongation per section of the drug label, by the message on QT prolongation in the SPC.

Table 2
Information and advices on QT prolongation reported in the drug label according to the message on QT prolongation according to the drug label ($n = 44$)

| Information and advice on QT prolongation | Nature of the message on QT prolongation | | | | |
|---|---|---|---|---|---|
| | All | Drug does not prolong QT | Unclear if drug prolongs QT | Drug possibly prolongs QT | Drug prolongs QT |
| | 44 (100%) | 10 (23%) | 19 (43%) | 7 (16%) | 8 (18%) |
| *Advice to act with caution or contraindicated in patients with risk factors related to QT prolongation:* | *27 (62%)* | *1 (10%)* | *11 (56%)* | *7 (100%)* | *8 (100%)* |
| Patients who have or may develop a prolonged QT | 18 (41%) | 0 | 6 (32%) | 5 (71%) | 7 (88%) |
| Patients with congenital long QT-syndrome | 16 (36%) | 0 | 6 (32%) | 6 (86%) | 4 (50%) |
| Patients with a family history of congenital long QT-syndrome | 4 (9%) | 1 (10%) | 1 (5%) | 2 (29%) | 0 |
| Concurrently with other drugs that prolong the QT-interval or anti-arrhythmics | 24 (55%) | 1 (10%) | 10 (53%) | 5 (71%) | 8 (100%) |
| Patients with electrolyte disturbances | 14 (32%) | 0 | 5 (26%) | 3 (43%) | 6 (75%) |
| Patients with bradycardia | 8 (18%) | 0 | 3 (16%) | 3 (43%) | 2 (25%) |
| Patients with cardiac disease | 15 (34%) | 1 (10%) | 6 (32%) | 4 (57%) | 4 (50%) |
| *Explaining the association of QT prolongation with ventricular arrhythmia, Torsade de Pointes, and sudden cardiac arrest* | *7 (16%)* | *0* | *2 (11%)* | *1 (14%)* | *4 (50%)* |
| *Advice on monitoring of patients using the product* | *15 (34%)* | *0* | *4 (21%)* | *4 (57%)* | *7 (88%)* |
| ECG prior to administration should be considered | 8 (18%) | 0 | 1 (5%) | 2 (29%) | 5 (63%) |
| Monitoring with ECG's during treatment should be considered | 12 (27%) | 0 | 2 (11%) | 4 (57%) | 6 (75%) |
| Electrolyte disturbances should be corrected prior to treatment | 8 (18%) | 0 | 2 (11%) | 3 (43%) | 3 (38%) |
| Monitoring of electrolytes during treatment should be considered | 8 (18%) | 0 | 1 (5%) | 2 (29%) | 5 (63%) |
| If the QT interval is prolonged the product should be stopped | 4 (9%) | 0 | 1 (5%) | 0 | 3 (38%) |

Values are numbers (percentages).

## 4. Discussion

Our study shows that the extent and content of information on QT prolongation varies considerably between drug labels, and in 43% of the drugs that mention the QT interval in the SPC, no clear statement

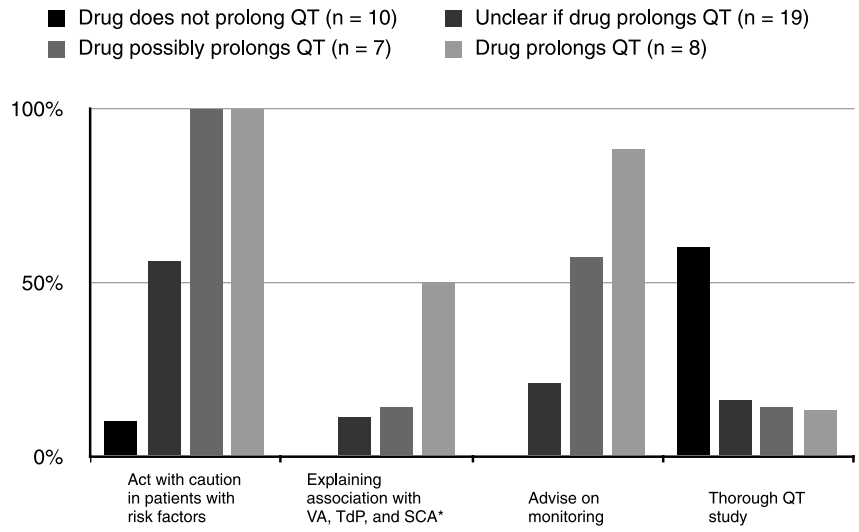


Fig. 3. Information on QT prolongation reported in the summary of product characteristics ($n = 44$).

on whether a drug prolongs the QT interval is mentioned in the SPC. Products that are more likely to have QT prolonging properties according to the SPC also provide more specific information on QT prolongation in other sections of the SPC.

Almost half of the SPCs that reported on QT prolongation, did not present a clear conclusion whether the drug induces QT prolongation, which is noteworthy. According to the guideline on summary of product characteristics the SPC or drug label is considered 'the basis of information for healthcare professionals on how to use the medicinal product safely and effectively' and 'the SPC should be worded in clear and concise language' [7]. The ICH E14 European Medicine Agency (EMA) guideline on the clinical evaluation of QT prolongation and proarrhythmic potential which aims to promote drug safety and prevent drug-induced sudden cardiac death [6], contains a short section on labeling issues for drugs that prolong the QT interval. It recommends that the following is considered: a warning/precautionary statement about the risk; a description of the design and results of the trials investigating the effect on the QT/QTc interval, including the absence of demonstrated effect; the dosage recommendations; a list of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, Long QT Syndrome, hypokalaemia); a precautionary statement regarding the concomitant use of two or more QT/QTc interval prolonging drugs and other interactions increasing the risk; recommendations for patient monitoring (ECG and electrolytes) and management of patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia' [6]. However, no guidance on how to formulate the message on QT prolongation is included. It is also not explicitly recommended to include an interpretation of the results, rather than a summary of the findings of the various trials.

We recommend to further update the ICH E14 guidelines to ensure more structured wordings on QT prolongation. In addition, we recommend an unambiguous interpretation of evidence, resulting in a clear 'message' on whether or not the products prolongs the QT, since the plain numbers of results of the trials investigating the effect on the QT interval may be hard to interpret for prescribing physicians. In addition,

we recommend to present the associations between QT prolongation and ventricular arrhythmia, torsade de pointes, and sudden cardiac arrest more explicitly in the drug label. Only a minority of the SPCs (16%) provides such information. To reduce the risk of torsade de pointes and sudden cardiac arrest, physicians should be aware that a prolonged QT interval is a potential indicator of cardiovascular risk. Importantly, a study of Al-Khatib et al. showed that the knowledge on QT prolongation among health care providers is still unsatisfactory, illustrating the importance of clear and concise information in the SPC [12].

According to Bastholm Rahmner et al. there is a need for databases that provide consistent information about new and existing drugs [13]. Inconsistencies in the SPC information undoubtedly reduce the utility of such systems when incorporating in these databases. Moreover, a more structured wording of the SPC on QT prolongation renders the recommendations in the SPC suitable for electronic prescribing systems and clinical decision support systems [14, 15].

We conclude that the extent and content of information on QT prolongation varies considerably between drug labels, and that in almost half of the drugs that mention the QT interval in the SPC, no clear statement on whether a drug prolongs the QT interval is mentioned in the SPC. The SPC is an important, albeit indirect, source of information for health care providers. Ambiguous information may hamper the usefulness of the information for prescribing physicians and lead to suboptimal risk minimization strategies. We therefore advocate to provide more structured phrasing of information and unambiguous interpretation of evidence on QT prolongation in the drug label, and provide clear instructions for prescribers how to deal with such risk.

## Competing interests

None of the authors declare an conflict of interest. Frank A Holtkamp, Peter GM Mol, and Marie L De Bruin are also (part-time) employees of the Dutch Medicines Evaluation Board (CBG-MEB). The views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the CBG-MEB.

## Funding

This work was supported by the Utrecht University. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## References

[1] Cubeddu L. QT prolongation and fatal arrhythmias: A review of clinical implications and effects of drugs. Am J Ther. 2003;10:452-7.
[2] Kramer D, Zimetbaum P. Long-QT syndrome. Cardiol Rev. 2011;19:217-25.
[3] Stockbridge N, Morganroth J, Shah RR, et al. Dealing with global safety issues: Was the response to QT-liability of non-cardiac drugs well coordinated? Drug Saf. 2013;36:167-82.
[4] Mol PG, Straus SM, Piening S, et al. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf. 2010;33:463-74.
[5] Guidance for Industry, E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005; Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf. Accessed March, 2013.

[6] Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonarrhythmic drugs (CHMP/ICH/2/04). 2005; Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf. Accessed March, 2013.
[7] A guideline on summary of product characteristics (SmPC). 2009; Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf. Accessed March, 2013.
[8] Why look at an SPC? Drug Ther Bull. 2009;47:56-8.
[9] European Medicines Agency database of European public assessment reports. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp. Accessed March, 2013.
[10] Markovaara J, Oxlade N, Williams R. Scrip's pharmaceutical company league tables 2008. http://www scripnews com/multimedia/archive/00042/Scrip_League_Tables_42249a xls, accessed on March 2013.
[11] Putzeist M, Mantel-Teeuwisse AK, Gispen-De Wied CC, et al. Regulatory scientific advice in drug development: Does company size make a difference? Eur J Clin Pharmacol. 2011;67:157-64.
[12] Al-Khatib SM, Allen LaPointe NM, Kramer JM, et al. A survey of health care practitioners' knowledge of the QT interval. J Gen Intern Med. 2005;20:392-6.
[13] Bastholm Rahmner P, Andersen-Karlsson E, Arnhjort T, et al. Physicians' perceptions of possibilities and obstacles prior to implementing a computerised drug prescribing support system. Int J Health Care Qual Assur Inc Leadersh Health Serv. 2004;17:173-9.
[14] Rubrichi S, Quaglini S. Summary of Product Characteristics content extraction for a safe drugs usage. J Biomed Inform. 2012;45:231-9.
[15] Rubrichi S, Quaglini S, Spengler A, et al. A system for the extraction and representation of summary of product characteristics content. Artif Intell Med. 2013;57:145-54.

Appendix 1

Information on QT prolonging properties mentioned in the drug label, categorised into four subsets, based on the phrasing used to report on the degree of QT prolonging properties of the compound

**Drug does not prolong QT interval**

– No events of clinically relevant QT prolongation have occurred (at supra-therapeutic or therapeutic doses, in clinical studies)

**Unclear if the drug does prolong the QT interval**

– Preclinical studies suggest that the drug has the potential to prolong the QT interval (Clinical studies: not stated or no (clinically relevant) effect on QT prolongation)
– Label contains conflicting statements on QT prolongation
– Events of QT prolongation have occurred, only at supra-therapeutic doses
– Numbers of events of QT prolongation occurred in clinical studies are stated, but no conclusion is drawn or interpretation is given concerning the ability to cause QT prolongation
– Label mentions QT prolongation only in section 4.8 in tabulated summary of adverse reactions
– Label does only mention warnings ("contra-indicated or use with caution when the patient has risk factors for QT prolongation")

**Drug does potentially prolong QT interval**

– Events of QT prolongation have occurred in clinical studies, but the clinical significance of this prolongation is unknown
– Few clinically relevant events of QT prolongation have occurred in clinical studies
– Events of QT prolongation have occurred in clinical studies, so an effect on QT interval cannot be ruled out

**Drug does prolong QT interval**

– Dose and/or concentration-related increases in the QT interval have been observed
– Events of QT prolongation have occurred (in clinical studies, at therapeutic doses)

Appendix 2

List of included products which mentioned QT in the SPC ($n = 44$) according to the message on QT prolongation in the SPC

| Not QT prolonging<br>$N = 10$ | Unclear drug-QT association<br>$N = 19$ | Possibly QT prolonging<br>$N = 7$ | QT prolonging<br>$N = 8$ |
|---|---|---|---|
| aliskiren | amifampridine | fingolimod | dronedarone |
| asenapine maleate | boceprevir | lapatinib | nilotinib |
| azilsartan medoxomil | darunavir | pasireotide | pazopanib |
| indacaterol | dasatinib | ranolazine | retigabine |
| methylnaltrexone | degarelix | tacrolimus | sorafenib tosylate |
| prucalopride | eltrombopag | telaprevir | sunitinib |
| saxagliptin | eribulin | vinflunine ditartrate | vandetanib |
| sitagliptin | fampridine | | vemurafenib |
| sugammadex | fesoterodine | | |
| trabectedin | gadoversetamide | | |
| | gefitinib | | |
| | lenalidomide | | |
| | maraviroc | | |
| | olanzapine | | |
| | paliperidone | | |
| | regadenoson | | |
| | rilpivirine | | |
| | telavancin | | |
| | vernakalant | | |

SPC: summary of product characteristics.