November 30, 2006

NOTICE

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Release of final Health Canada document: QT/QTc Interval Prolongation: Guidance for Product Monograph Content

On April 5, 2006, Health Canada adopted the following two International Conference on Harmonisation (ICH) guidances:

- ICH S7B: The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
- ICH E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Health Canada has developed the following regional guidance documents to support the interpretation and implementation of these guidances:

- Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances
- Guide for the Analysis and Review of QT/QTc Interval Data
- QT/QTc Interval Prolongation: Guidance for Product Monograph Content

The document entitled *QT/QTc Interval Prolongation: Guidance for Product Monograph Content* sets forth standardized Product Monograph content for drugs with QT/QTc prolongation potential to ensure that relevant safety information is available for health professionals and patients. This document is intended to assist the pharmaceutical industry in preparing and revising Product Monographs for drugs for which QT/QTc prolongation labelling is warranted.

The approach for implementing this guidance is as follows: All sponsors who market drugs for which QT/QTc prolongation labelling is warranted should, upon filing of a drug submission to Health Canada, ensure that their labelling is in accordance with this guidance. Adherence to this Guidance for Product Monograph Content is expected for applicable submissions as of April 1, 2007. It is recognized that, for some marketed drugs, the types of data specified in this guidance document will not be available. In these cases, the sponsors should comply with the guidance to the extent possible.

This document replaces the draft guidance document of the same title. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document. A tabulation summarizing the comments received during the external consultation and the outcome of the Health Canada discussion of these comments is available on request.

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Should you have any questions or comments regarding the content of this guidance, please contact :

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Health Canada Santé Canada

GUIDANCE DOCUMENT

QT/QTc Interval Prolongation: Guidance for Product Monograph Content

Published by authority of the
Minister of Health

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Health Products and Food Branch

Canada

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Également disponible en français sous le titre : Allongement de l'intervalle QT/QTc: Contenu des monographies de produit

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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TABLE OF CONTENTS

1. INTRODUCTION

1.1 Background

The QT interval of the surface electrocardiogram (ECG) consists of the QRS complex, which represents depolarization within the His-Purkinje system and ventricles, and the JT interval, which reflects ventricular repolarization. The QT interval is measured from the initiation of the QRS complex to the termination of the T wave. Because of its inverse relationship to heart rate, the measured QT interval is routinely transformed by means of various heart rate correction formulae into a variable known as the corrected QT interval (QTc) that is intended to be independent of heart rate.

Excessive prolongation of the QT/QTc interval creates an electrophysiological environment that is conducive to torsade de pointes, a polymorphic ventricular tachyarrhythmia that can result in syncope or progress to ventricular fibrillation and sudden cardiac death. Torsade de pointes appears on the ECG as continuous twisting of the QRS complex around the isoelectric line.

Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, can be the basis for non-approval of a drug or discontinuation of its clinical development. Failure to perform an adequate clinical assessment of the QT/QTc prolongation potential of a drug may likewise be justification to delay or deny marketing authorization.

The risk-benefit assessment of a QT/QTc-prolonging drug will take into account the morbidity and mortality associated with the untreated disease or condition, the clinical significance of the beneficial effects, and the magnitude of the QT/QTc interval prolongation. Considerations that will have a negative impact on the risk-benefit assessment include the availability of therapeutic alternatives that are otherwise similar in terms of safety and efficacy, but lack QT/QTc prolongation effects or prolong the QT/QTc interval to a lesser degree. If QT/QTc prolongation is a feature shared by other drugs of the therapeutic class in question, the risk-benefit assessment will involve a comparison of the effects observed with the new drug to those of its class members in concurrent active control groups. The demonstration of therapeutic benefits in patients refractory to, intolerant of, or not candidates for available therapies might justify the approval of a QT/QTc-prolonging drug, if its indication were limited to use in such patients.

Concerns would be accentuated by a steep concentration-effect relationship that would make dosing errors or normal inter-individual variability particularly dangerous. Drugs with primary metabolic pathways involving enzymes that are subject to genetic polymorphisms (*e.g.*, CYP2D6, CYP2C19) or inhibition by many drugs (*e.g.*, CYP3A4) would be regarded with particular concern, because of the risk of markedly elevated plasma levels in poor metabolizers or in the presence of interacting xenobiotics. A susceptibility to drug-drug interactions at the level of transporter proteins would also have a negative impact on the risk-benefit assessment.

The utility and feasibility of risk management options are important final considerations in rendering a decision about the approvability of a drug that prolongs the QT/QTc interval. A major component of risk mitigation and communication is the inclusion of appropriate prescribing information in the Product Monograph for a new drug.

1.2 Objectives

This document is intended to provide guidance to the pharmaceutical industry, the Therapeutic Products Directorate, and the Biologics and Genetic Therapies Directorate concerning the expected Product Monograph content for drugs that prolong the QT/QTc interval in humans. This document should be used in association with the following guidelines:

- Health Canada Guidance Document: Product Monograph. October 1, 2004.
- International Conference on Harmonisation S7B Guideline: The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. May 12, 2005.
- International Conference on Harmonisation E14 Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. May 12, 2005.
- Health Canada Guidance Document: Guide for the Analysis and Review of QT/QTc Interval Data. September 6, 2006.

1.3 Scope

The recommendations contained in this guidance document are applicable to drugs for which evidence of QT/QTc prolongation in humans is considered to justify concern with respect to proarrhythmic potential. Regulatory decisions regarding approval and prescribing information should be based on a careful assessment of relevant data from all stages of drug development,

with appropriate attention to evidence of dose-dependency, concentration-relationship, and trend-over-time; central tendency analyses of magnitude of effect; categorical analyses of outlier values; morphological abnormalities; discontinuations and dosage reductions due to QT/QTc prolongation; and pre- or post-marketing adverse events suggestive of proarrhythmia. This guidance document is intended primarily for new drugs with systemic bioavailability, but might also be applicable to marketed products, if concerns have emerged or intensified on the basis of new clinical trials or post-marketing experience.

1.4 QT/QTc Interval Prolongation: Implications for the Product Monograph

If the risk-benefit assessment of a QT/QTc-prolonging drug is considered to support approval, careful attention should be directed to the content of the Product Monograph to ensure that risks and their attendant mitigation strategies are clearly communicated. In the sections that follow, recommendations are provided concerning health professional information, scientific information, and consumer information to be included in the Product Monographs of drugs that prolong the QT/QTc interval as an unintended collateral effect.

2. PART I HEALTH PROFESSIONAL INFORMATION

2.1 Indications and Clinical Use

If the overall risk-benefit assessment leads to the conclusion that safer therapeutic options are available for the indication in question, it might be appropriate to limit the use of a QT/QTc-prolonging drug to patients who are refractory to, intolerant of, or not candidates for other therapeutic modalities. The following sample text is provided:

> *Because of concerns about QT/QTc prolongation and associated arrhythmia, the use of <brand name> should be limited to patients who are refractory to, intolerant of, or not candidates for other therapeutic modalities. Clinical trials specifically designed to characterize the safety and efficacy of <brand name> in these populations have not been performed.*

Assessment of relative QT/QTc prolongation potential should be undertaken with caution in the absence of clinical trials with concurrent comparator groups. Such assessments may not be possible when ECG safety data for comparator products are lacking or were collected and analysed under different conditions.

2.2 Contraindications

If use of the drug in patients with certain diseases or disorders or in combination with interacting medications would be expected to pose a risk of arrhythmia that outweighs any potential therapeutic benefit, then contraindications should be provided for the conditions or interacting drugs in question (see 'Warnings and Precautions' and 'Drug Interactions' below). Cross-references should be provided to more detailed information on drug-drug or drug-disease interactions in the 'Warnings and Precautions' or 'Drug Interactions' section.

2.3 Warnings and Precautions

2.3.1 Cardiovascular

A warning/precautionary statement should be provided about the effects of the drug on cardiac repolarization. The following text is recommended:

> *<Brand name> is associated with QT/QTc interval prolongation (see Part I Action and Clinical Pharmacology and Part II Clinical Trials)[1]. Many drugs that cause QT/QTc prolongation are suspected to increase the risk of a rare polymorphic ventricular tachyarrhythmia known as torsade de pointes. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.*

When justified by the risk assessment, this information should be presented in a 'Serious Warnings and Precautions Box' for greater emphasis.

Cross-references should be provided to information relating to QT/QTc interval prolongation that appears in other parts of the Product Monograph.

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[1] If the Product Monograph is being revised on the basis of post-marketing experience, in the absence of reliable ECG data, the first sentence could be modifed as follows: A) *<Brand name> may be associated with QT/QTc interval prolongation.* B) *Some drugs of <chemical/ pharmacological class> cause QT/QTc interval prolongation. <Brand name> has not been studied for this effect, but might have this problem as well.*

Depending on the estimated level of risk posed by the new drug, contraindications (see 'Contraindications' section above) or warnings and precautions should be provided for patients with diseases or disorders that are known or suspected to increase the possibility of arrhythmic events:

[Particular care should be exercised when administering <brand name> to/Use of <brand name> should be avoided in] patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QT/QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following:

- *female*
- *age 65 years or older*
- *baseline prolongation of the QT/QTc interval*
- *presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes*
- *family history of sudden cardiac death at <50 years*
- *cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease)*
- *history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)*
- *electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)*
- *bradycardia (<50 beats per minute)*
- *acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma)*
- *nutritional deficits (e.g., eating disorders, extreme diets)*
- *diabetes mellitus*
- *autonomic neuropathy*
- *hepatic dysfunction, renal dysfunction, and/or phenotypic/ genotypic poor metabolizers of drug metabolizing enzyme isoforms, if relevant to the elimination of the drug*

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

2.3.2 Monitoring and Laboratory Tests

When justified by the magnitude of the observed QT/QTc prolongation effect, recommendations for screening ECGs may be warranted. In general, treatment with a drug that causes QT/QTc prolongation should not be initiated in patients with abnormally long baseline QTc intervals. Monitoring of the QT/QTc interval during treatment may also be advisable, particularly during the initial stages of treatment, after a dosage increase, or for drugs administered intravenously. Discontinuation of the drug should be encouraged if symptoms suggestive of arrhythmia occur or if the QT/QTc interval becomes markedly prolonged.

Measurement of serum potassium, calcium, and magnesium levels may be advisable prior to initiation of treatment with a drug that prolongs the QT/QTc interval. Monitoring of serum electrolyte levels during treatment might also be appropriate, with prompt correction of the imbalance and/or discontinuation of the QT/QTc-prolonging drug in the event of an electrolyte abnormality.

2.4 Adverse Reactions

In the 'Adverse Drug Reaction Overview', attention should be directed to any events of sudden death, torsade de pointes, ventricular fibrillation or flutter, cardiac arrest, or other serious adverse events suggestive of proarrhythmia that were reported in the New Drug Submission safety database.

If any of the aforementioned events were reported in Phase IV clinical trials or through post-market surveillance, these should be tabulated or listed under 'Post-Market Adverse Drug Reactions'.

2.5 Drug Interactions

2.5.1 Drug-Drug Interactions

Attention should be directed to any drug-drug interactions that would be expected to result in an exaggerated prolongation of the QT/QTc interval. Presentation of this information in the 'Serious Drug Interactions Box' will provide increased emphasis, when the level of risk is judged to be considerable:

> *The concomitant use of <brand name> with another QT/QTc-prolonging drug is <contraindicated/discouraged>. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:*
>
> - *Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)*

- *Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)*
- *Class 1C antiarrhythmics (e.g., flecainide, propafenone)*
- *antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol)*
- *antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline)*
- *opioids (e.g., methadone)*
- *macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin)*
- *quinolone antibiotics (e.g., moxifloxacin, gatifloxacin)*
- *pentamidine*
- *antimalarials (e.g., quinine)*
- *azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)*
- *domperidone*
- *5-HT_3 antagonists (e.g., dolasetron, ondansetron)*
- *tacrolimus*
- *beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)*

<Brand name> is a substrate for <metabolizing enzyme/transporter>. Plasma levels of <parent compound> can be increased by inhibitors of <metabolizing enzyme/transporter>. Prolongation of the QT/QTc interval by <brand name> is <known/anticipated> to be increased in the presence of <metabolizing enzyme/transporter> inhibitors. Drugs that inhibit <metabolizing enzyme/transporter> include <examples>. The concomitant use of these drugs with <brand name> is <contraindicated/discouraged>[2]*.*

<Brand name> is, itself, an inhibitor of <metabolizing enzyme/transporter>. <Brand name> is <known/anticipated> to <decrease the metabolism/increase the bioavailability> of the following drugs that also prolong the QT/QTc interval: <examples>. The concomitant use of these drugs with <brand name> is <contraindicated/discouraged>.

The use of <brand name> is <contraindicated/discouraged> with drugs that can disrupt electrolyte levels, including, but not limited to, the following:

- *loop, thiazide, and related diuretics*
- *laxatives and enemas*
- *amphotericin B*
- *high dose corticosteroids*

[2] If the parent compound and its metabolites have similar QT/QTc prolongation liability, the presence of metabolic inhibitors might not affect the magnitude of QT/QTc prolongation, in which case the above paragraph should be revised accordingly.

The following statements should follow these lists:

> *The above lists of potentially interacting drugs are not comprehensive. Current scientific literature should be consulted for newly approved drugs that prolong the QT/QTc interval, inhibit <metabolizing enzyme/transporter>, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.*

If a particular drug-drug interaction has been studied in clinical trials, the results of the trial should be summarized briefly in this section.

2.5.2 Drug-Food Interactions

If the plasma concentrations of a QT/QTc-prolonging drug can be increased by a drug-food interaction (*e.g.*, inhibition of CYP3A4 by grapefruit juice), any such interactions should be described.

2.6 Dosage and Administration

When possible, dosage recommendations should encourage the use of the lowest effective dose of the drug and specify maximum recommended single and total daily doses that should not be exceeded. Restrictions on the size and frequency of incremental dose adjustments might be appropriate. In some cases, it might also be useful to identify a time after which the drug should be discontinued, if satisfactory efficacy has not been achieved. For an intravenously administered drug that prolongs the QT/QTc interval, limitations on the injection and/or infusion rates may be critical.

2.7 Overdosage

The risk of torsade de pointes with a QT/QTc-prolonging drug is usually dose-dependent. Recommendations for continuous ECG monitoring are often appropriate in cases of overdose with drugs that prolong the QT/QTc interval. Strategies for the treatment of torsade de pointes and ventricular fibrillation can be an important component of the instructions for the management of overdosage.

2.8 Action and Clinical Pharmacology

2.8.1 Pharmacodynamics

The 'Pharmacodynamics' sub-section should provide a concise summary of the clinical pharmacology studies that were designed to characterize drug-related increases in the QTc interval. This summary should include information on the design (*e.g.*, parallel group, crossover, incomplete crossover), sample size, whether the subjects were healthy volunteers or patients, the age and gender of the subjects, the doses studied, and the duration of treatment.

The QTc data for therapeutic doses and supratherapeutic doses, as well as positive controls and reference treatments, should be presented in the form of a time profile plot in which the baseline- and placebo-adjusted QTc interval is plotted as a function of time, with two-sided 90% confidence intervals. A legend should be provided that identifies the treatments represented by the symbols used in the plot (*e.g.*, drug, dose, and multiple of maximum recommended dose). To provide for consistency between Product Monographs, QTc data corrected for heart rate by Fridericia's formula should be provided. If the sponsor can demonstrate that Fridericia's formula is not the optimal heart rate correction for the data set in question, QTc data corrected by a study population-specific heart rate correction may be provided as well in a parallel plot. A footnote explaining the heart rate corrections used should be provided (*e.g., QTc values are corrected for heart rate using Fridericia's formula [*$QTc=QT/RR^{0.33}$*] and a study population-specific correction [*$QTc=QT/RR^{0.39}$*]).* The figure should be preceded by the following statements:

> *The magnitude of QTc prolongation observed in a clinical trial will depend on the study conditions, such as the subject population, the dose and duration of treatment, the equipment used, and the methods employed for reading the ECGs and analysing the QTc data. For this reason, QTc data from different clinical trials are not suitable for direct comparison in terms of magnitude of effect.*

A tabulation summarizing the number and incidence of outlier values should be provided when warranted by the observed effects.

QTc interval data from clinical pharmacology studies in patients or sub-populations of interest, such as pediatrics, geriatrics, subjects with renal or hepatic insufficiency, or genetic polymorphisms, should be presented in this section as well, whenever these provide useful additional information. Data on the magnitude of the QTc prolongation effect in the special population relative to healthy adult volunteers would be of particular interest.

3. PART II SCIENTIFIC INFORMATION

3.1 Clinical Trials

This section should generally include a summary of the integrated analyses of QT/QTc data from the therapeutic clinical trials. ECG data should be pooled only from studies in which the evaluations were performed with similar rigour (*e.g.*, sampling frequency). When possible, the

new drug should be compared with a placebo treatment arm, with attention to the point estimate and the upper bound of the two-sided 90% confidence interval. Comparisons with active control treatments are also important, especially if a placebo group is unavailable. Presentation of the mean time-averaged change from baseline would be acceptable only for studies in which the ECG recordings were obtained during fixed dose treatment under steady-state conditions, with no evidence for a sustained increase or decline in the effect over the course of continued treatment. In some cases, conclusions based on data for a particular time point might be acceptable, if supported by a convincing rationale (*e.g.*, single dose parenteral use; short duration of treatment, with only one ECG assessment performed at steady-state; or very long duration of treatment, such that ECGs at late time points are unlikely to be comparable to baseline ECGs due to progression of the underlying disease process). In other cases, the mean of the maximum individual on-therapy increases from baseline may be the most informative endpoint. QT/QTc data for the change from baseline to final evaluation will not be suitable for inclusion in this section, if they include ECGs collected after the last day of treatment with the study drug.

As the ECG sampling frequency in therapeutic clinical trials is seldom sufficient to accurately characterize maximum effects, this section should be prefaced by the following statements:

> *ECG recordings were performed in these trials at <weekly/biweekly/ monthly> intervals. The ECG recordings were performed at <X h post-dosing/random time points in relation to dosing>. Due to the low ECG sampling frequency, these data are not expected to reflect the maximum effect of the drug on the QTc interval. For studies that were designed to quantify the maximum QTc prolongation, see 'Action and Clinical Pharmacology, Pharmacodynamics'. The magnitude of QTc prolongation observed in a clinical trial will depend on the study conditions, such as the subject population, the dose and duration of treatment, the equipment used, and the methods employed for reading the ECGs and analysing the QTc data. For this reason, QTc data from different clinical trial programmes are not suitable for direct comparison in terms of magnitude of effect.*

3.2 Detailed Pharmacology

This section should contain a brief summary of the results of the nonclinical safety pharmacology studies that were performed to assess the potential of the drug to delay cardiac repolarization. In some cases, studies performed with active metabolites or resolved enantiomers may be important, in addition to those performed with the parent compound or racemate.

For studies of hERG or I_{Kr} ion channels, the following information should be provided:

- test system: expression system (specify cell line) or disaggregated cardiac myocytes (specify species)
- sample size
- positive study: 50% inhibitory concentration (IC_{50}) for suppression of the peak amplitude of the tail current (or the $IC_{20/30/40}$, if 50% inhibition was not attained at the highest feasible concentration)
- negative study: the highest tested 'no effect' concentration should be specified, with a rationale for the choice of the upper limit of the concentration range
- potency estimates for concurrent positive controls and/or reference compounds
- statement regarding whether the reported concentrations are nominal or experimentally verified

Corresponding information should be provided for any other ion channel assays that were performed (*e.g.*, SCN5A or I_{Na}, KvLQT-MinK or I_{Ks}).

Comparison of *in vitro* potency estimates with free or total therapeutic plasma concentrations is not considered to be appropriate in the Product Monograph.

For *in vivo* assays of QT/QTc prolongation potential, the following information should be provided, preferably in a tabular format:

- species/gender
- sample size
- design (*e.g.*, crossover, parallel group, escalating dose)
- conscious or anaesthetized (state anaesthetic used)
- free-moving or restrained
- telemetry, conventional ECG leads, or Holter ECGs
- dose range (with rationale)
- single dose/repeat dose
- administration route
- time points studied
- magnitude of the maximum mean QTc increase from baseline for the test substance and time-matched vehicle control or an alternative estimate of the peak increase, if demonstrated to be more informative
- corresponding data for any concurrent positive controls and/or reference compounds
- plasma concentrations, if available
- occurrence of arrhythmias or arrhythmic deaths

A summary of any repolarization assays that were performed would also be appropriate in this section. The test system(s) should be described (*e.g.*, studies of transmembrane action potentials in isolated cardiac myocytes, papillary muscles, or Purkinje fibres or studies of monophasic action potentials in Langendorff-perfused isolated heart or anaesthetized animals). The laboratory species from which the preparations were derived should be stated. The concentration or dose range studied should be specified, with a statement regarding whether the reported *in vitro* concentrations are nominal or experimentally verified. Parameters that might provide useful information on proarrhythmic potential include the action potential duration at 90% repolarization, action potential amplitude, and the maximal rate of depolarization. The occurrence of early afterdepolarizations and/or triggered activity should be noted.

The results of any studies using proarrhythmia models may be included as well, with information regarding the test system, doses studied, and the incidence of arrhythmias observed with the test drug relative to vehicle and positive control groups.

3.3 Toxicology

Information on QT/QTc prolongation, cardiac arrhythmias, or sudden deaths from toxicology studies should be presented in this section.

4. PART III CONSUMER INFORMATION

4.1 About this Medication

If the approved indication for a QT/QTc-prolonging drug is limited to patients who are refractory to, intolerant of, or not candidates for alternative therapies, the sub-section entitled 'What this medication is used for' should contain the following statement:

> *<Brand name> should be used when potentially safer alternatives are considered unsuitable.*

4.2 Warnings and Precautions

The 'Warnings and Precautions' section should contain an explanation in lay language of the effect of the drug on the electrical activity of the heart and the relationship between this ECG effect and the theoretical or demonstrated risk of arrhythmias and sudden death. Presentation of this information in the 'Serious Warnings and Precautions Box' will often be appropriate. The following text is suggested:

<Brand name> has an effect on the electrical activity of the heart. This effect can be measured as a change in the electrocardiogram (ECG)[3]*. In <infrequent/rare/very rare> cases, drugs with this effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. In general, females and people more than 65 years in age are at higher risk. It is important to follow the instructions of your doctor with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.*

The following items should be included in the list of considerations to discuss with the health care professional, before initiating use of a drug that causes QT/QTc interval prolongation:

Before you use <brand name>, talk to your doctor or pharmacist if you have:

- *a disorder known as Long QT Syndrome*
- *heart disease*
- *a personal history of fainting spells*
- *a family history of sudden cardiac death at <50 years*
- *electrolyte disturbances (e.g., low blood potassium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)*
- *an eating disorder or are following a strict diet*
- *diabetes, especially with associated nerve disorders*
- *liver/kidney disease (if relevant to the elimination of the drug)*

Any risk management strategies recommended for the drug should be described in this section:

<Electrocardiograms (ECGs)/Blood tests> may be required periodically to monitor the risk of potentially serious side effects during treatment with <brand name>.

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[3] If the Product Monograph is being revised on the basis of post-marketing experience, in the absence of reliable ECG data, the first two sentences of this paragraph could be modified as follows: A) *<Brand name> may have an effect on the electrical activity of the heart. Effects of this type can be measured as a change in the electrocardiogram (ECG).* B) *Some drugs of <chemical/ pharmacological class> have an effect on the electrical activity of the heart. Effects of this type can be measured as a change in the electrocardiogram (ECG). <Brand name> has not been studied for this type of effect, but might have this problem as well.*

4.3 Interactions with this Medication

A list of medications known or anticipated to interact with the QT/QTc-prolonging drug should be provided, including the following:

- drugs known to prolong the QT/QTc interval and/or cause torsade de pointes
- drugs that decrease electrolyte levels
- drugs that decrease the metabolism of <brand name>, assuming that the parent compound has greater QT/QTc interval prolongation liability than its metabolites
- drugs that increase the bioavailability of <brand name>
- if <brand name> is, itself, an inhibitor of one or more drug metabolizing enzymes, other drugs known to prolong the QT/QTc interval that would be subject to substantial metabolic inhibition in the presence of <brand name>

This list should be prefaced by the following statements:

> *The following list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems while receiving <brand name>. You should check with your doctor or pharmacist before taking any other medication with <brand name>.*

Any known or suspected drug-food interactions should also be listed here (*e.g.*, grapefruit juice, if <brand name> is metabolized primarily by CYP3A4).

4.4 Proper Use of this Medication

Drug-induced QT/QTc prolongation is usually dose-dependent. This section should contain the following statements:

> *Dosage directions should be followed carefully. Never exceed the prescribed dose.*
>
> *If you take more than the recommended number of <tablets/capsules>, call your doctor or a poison control centre immediately.*

4.5 Side Effects and What to Do About Them

The following text should be provided in this section:

> *If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.*

These adverse events should also be listed in the tabular portion of this section, as applicable.

For some drugs it may be appropriate to recommend that the patient stop treatment until a physician has determined whether it is safe to resume.

5. CONCLUSIONS

While the Product Monograph has an important role in risk communication and mitigation, it is important to recognize that the recommendations contained therein can be expected to reduce, but not eliminate, the occurrence of serious arrhythmic adverse events associated with drugs that cause QT/QTc interval prolongation. The advice provided in this guidance document is intended to achieve risk reduction by promoting informed and appropriate drug use by prescribers, dispensers, and consumers.

Decisions regarding the approvability of drugs that possess the potential to delay cardiac repolarization are based on a complex consideration of the risks and benefits associated with the product. The inclusion of contraindications, dosage restrictions, and other precautionary material in the Product Monograph will not necessarily represent an adequate risk mitigation strategy.

The acquisition, reading, and analysis of QT/QTc data are currently subjects of intensive discussion and research activity. The recommendations contained in this guidance document might undergo modification in the future to reflect new developments in these areas.