International Reporting of Periodic Drug-Safety Update Summaries

Final Report of CIOMS Working Group II

CIOMS

Geneva, 1992

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ACKNOWLEDGEMENTS

The Council for International Organization of Medical Sciences is greatly indebted to the members of the CIOMS Working Group on International Reporting of Periodic Drug Safety Update Summaries, and the drug regulatory authorities and pharmaceutical companies they represented, for the efficient and expeditious way in which they brought this project to its successful conclusion. Special thanks are due to the co-chairpersons, Drs B. Bruppacher, W.M. Castle, G.A. Faich and B. Wiholm, for their enthusiasm and leadership in conducting the project and preparing the final report. Thanks are also due to Dr S. Gallagher for his assistance in the editing of the final report.

VISION

It is the vision of the members of CIOMS Working Group II that the requirements for the international reporting of drug safety information will eventually be harmonized throughout the world.

To this end, the CIOMS Working Groups on Adverse Drug Reactions have devised the CIOMS Form for the expedited reporting of individual cases (Working Group I), and the CIOMS Report for aggregated safety information (Working Group II).

Recognising that several countries already have periodic reporting requirements for safety updates, the members unanimously support the view that the CIOMS Periodic Safety Reports should eventually supplant current requirements.

With respect to the expedited reporting of individual cases by pharmaceutical manufacturers, it is expected that the present domestic requirements will be maintained, and that the CIOMS initiative will flourish.

These two initiatives should contribute significantly to the harmonization of safety information for drug products and benefit in common the pharmaceutical industry and drug regulatory authorities.

INTRODUCTION

Drug regulatory agencies and pharmaceutical manufacturers have the task of making the use of medicines as effective and safe as possible. To do so, available international information must be consistently and appropriately analysed and reported. National regulatory agencies are therefore requiring increasing amounts of both foreign and domestic data, using the manufacturer as one international link. For manufacturers this can become a considerable burden, especially if countries differ in their requirements and if different authorities request that information from the same source be presented according to different inclusion criteria, formats and time intervals. Differences in numerical results may cause confusion.

Regulations can be made more functional if discussed openly, with a will to succeed, by representatives of all interested parties. The common goal is to make safety surveillance as useful and efficient as possible. The Council for International Organizations of Medical Sciences (CIOMS) provides a forum for manufacturers and regulators to work together to develop and test standard procedures. Between 1986 and 1989 a CIOMS working group on international reporting of adverse drug reactions (now called CIOMS Working Group I) developed a uniform approach and format for reporting, by manufacturers to regulatory authorities, suspected adverse drug reactions (ADR) occurring in foreign countries (International Reporting of Adverse Drug Reactions, Final Report of CIOMS Working Group, Geneva, 1990).

At a follow-up meeting held in Amsterdam in November 1989, a reconvened ADR working group, consisting of members of the first working group and others invited from industry and regulatory authorities, met to explore the possibility of developing harmonized or standardized approaches to safety-update summaries (Annex 1, Membership of CIOMS Working Group II). Such summaries could fill the needs of countries that lack the capacity to analyse single cases of ADR appearing in foreign countries, and at the same time provide a model of how such data could be presented so as to forestall any future diversity of safety-update regulations. This working group, called CIOMS Working Group II, was co-chaired by Drs Bruppacher, Castle, Faich and Wiholm.

The purpose of CIOMS Working Group II was not to compare present regulations. It was to provide a satisfactory way, using few resources, for companies to report safety information to regulatory bodies, and to elaborate uniform procedures that should meet most existing and future needs so that future regulatory requirements could be based on these procedures. The Group concentrated on safety updates required by many regulatory authorities periodically after a product is approved. It is in the interests of all concerned, industry and governments, to follow generally acceptable guidelines for these updates. If the guidelines are adequate and reasonable other health authorities will adopt them.

CIOMS Working Group I had focused on reports of adverse drug reactions occurring in countries foreign to the particular national regulatory authority, but for safety updates regulators require summary information from both domestic and foreign sources. A safety update by its nature is not an alert; rather, it should provide a review of information accumulated from the various sources since the previous report, put into context against previous information. Each regulator requiring an update would receive the same update summary at the

same time. Where necessary, it should be supplemented by important data received since the latest data lock-point (see definition of data lock-point, page 12). A new important safety issue should continue to be brought immediately to the attention of prescribing physicians through the regulatory authority, according to current procedures, which are not addressed in this report.

In the future, the same safety update format proposed here could be considered as a basis for periodic or final pre-marketing safety reports.

Comments are invited and should be sent to Dr Zbigniew Bankowski, Secretary-General, CIOMS, c/o WHO, avenue Appia, 1211 Geneva 27, Switzerland.

BACKGROUND

Present Regulations for Periodic Safety Updates

Regulations vary and a survey was conducted of safety-update reporting requirements in the nine countries whose national authorities were represented in CIOMS Working Group II. (The survey was conducted by Dr Arnold Gordon.) Information was obtained on whether these countries required periodic safety-update reports (1) before a marketing application dossier is submitted, (2) after submission but before a licence is granted, and (3) while a drug is on the market; and whether there was a formal requirement to conduct any type of formal post-marketing surveillance study as a condition of licensing. The summary results are found in Table 1A.

Only the United States of America has specific requirements for routinely supplying summary safety-update information prior to initial marketing application. The USA requires also pre-approval, post-submission reviews, and along with France, Germany and Italy formally requires periodic summaries post-launch. In the United Kingdom, the Committee on the Safety of Medicines (CSM) encourages the conduct of post-marketing surveillance (PMS) studies, but like the other eight regulators has no formal requirement, except possibly on an ad hoc basis. The survey was extended to include countries not represented in the Working Group: the data in Table 1B cover all other countries known to have some safety-update reporting requirements.

The focus of CIOMS Working Group II was on routine safety updates on marketed products. Table 1A shows that the timing for such reports varies considerably: for example: Italy — half yearly every year; Germany — two and five years post-launch, then every five years; France — half yearly for the first year, then annually; USA — quarterly for three years, then annually.

The survey also showed that not only does the frequency of reporting differ but also the nature and presentation of the data required are in some cases very different (Table 2). The US is alone in requiring two different types of reports, referred to as the NDA (New Drug Application) safety update ("quarterly") and the annual ("periodic") reports, both covering clinical experience; however, the latter does not focus on detailed safety data. These conditions make it very difficult for manufacturers to cope, especially when worldwide experience must be included. Among the types of information requested by various regulators, in addition to spontaneous report and trial data, are product registration status and important changes; modifications in labeling; drug exposure data; and published information in the literature. In the Netherlands the only information called for relates to changes in foreign registration affecting use of a drug.

The situation is further aggravated in that anniversary dates of licensing approval vary considerably among countries. Therefore manufacturers have difficulties in complying with the diverse scheduling demands because the different health authorities are receiving different types and amounts of data covering widely different time periods. This can cause considerable confusion in a regulatory environment where there is increasing cross-communication. This has special relevance to Europe in view of developments in the European Economic Community.

Table 1A: Requirements for Periodic Safety Updates (Countries represented in CIOMS Working Group II)

Country	Before submission of marketing application dossier	After submission, before approval	While drug marketed (Time post-launch, in years)	Formal post-marketing surveillance requirements
Canada	N	N	N	N
Denmark	N	N	N	N
France	N	N	0.5, 1.0, Yearly	M Local
Germany	N	N	2, 5; then every 5 years	N
Italy	N	N	January and July every year	N
New Zealand	N	Y*	N	Y**
Sweden	N	N	N	N
United Kingdom	M	N	N	Y "Voluntary"
United States of America	Y	Y	0.25 for 3 years; then yearly	M

Y = yes; N = no; M = maybe
* Often but not always requested by the Department of Health
** Only as requirement for reimbursement status approval

Table 1B: Requirements for Periodic Safety Update Reports (Countries not represented in CIOMS Working Group II)

Country	Before submission of marketing application	After submission, before approval	While drug marketed (Time post-launch in years)
Australia	N	N	Yearly for 3 years
Japan	N	N	Yearly; special 6-year report
Korea, Republic of	N	N	Yearly for 3 years
Netherlands	N	N	0.5 for 5 years then every 5 years
Philippines	N	Y	Yearly
Switzerland	N	N	0.5, 1.0*
Taiwan	N	N	0.5 for 3 years
Thailand	N	N	0.2 for 2 years
Proposed EC (1993)	N	N	0.5 for 2; Yearly for 3, then every 5, years

Y = yes; N = no
* Only for drugs approved under "monitored release"

Table 2: General Contents of Periodic Safety Reports on Marketed Products (1991)

Country	Registration status elsewhere	Market use statistics	Clinical trial data	Spontaneous reports
Australia	–	L	W	L
France	—	W	—	W
Germany	Yes	W	W	W
Italy	—	L	L	L
Japan	—	—	L	—
Korea, Republic of	—	—	—	L
Netherlands	Yes	—	—	—
Philippines	—	—	L	L
Switzerland	Yes	W	W	W
Taiwan	—	w	W	W
Thailand	—	L	L	L
US — quarterly* (314.80)	—	—	W	L
US — annual (314.81)	—	W	W +	—

L = local data only; W = worldwide data (local and foreign)

* Summary of serious, unlabelled, attributable clinical-trial cases; all US spontaneous reports; summary of all foreign serious, unlabeled reports; and examination of increased frequency of serious labeled events, including death, from all sources.

\+ Preclinical study information also required.

Important Questions

With the above considerations in mind, some of the important questions that CIOMS Working Group II had to answer in proposing a standardized safety-update summary were:

1. Which products should be covered (e.g. only those newly marketed)? (see page 13)
2. Should certain products be grouped together (dosage forms, combinations, different formulations), and how? (see page 14)
3. Should new Chemical entities (NCEs) and "old" medicinal products be handled differently? (see page 14)
4. When should data lock-points and dates of submitting safety-update summaries be? (see page 14)
5. What should be the source and the scope of the data to be included? How should the data be combined? (see page 15)
6. How much detail is required? (see page 15)
7. How should exposure data be defined and used? (see page 15)
8. Should increased frequency of known toxicity be addressed? (see page 18)

* * *

The group was not in a position to recommend new legislation on safety updates but it could propose practical and useful Solutions for current and relevant requirements. Discussion therefore related primarily to the best presentation of data considered important for routine safety updates. The aim of the group was to propose a general format that could be modified to meet somewhat different specific situations. It held six meetings over a two-year period. The reader is referred to Annexes 2-4 for details of discussions and how consensus was reached, and for an account of the pilot project and outstanding issues. The group knew it had to recommend a report specification which would be practicable and yet comprehensive in meeting regulatory requirements. Hence it recommended that the narrative content of the report should not exceed about 10 pages.

Annex 6 presents a fictitious example of a periodic safety update report. It was written in the CIOMS format by Mrs Sue Roden, Head of the Drug Review Group at Glaxo Group Research in Greenford, England.

DEFINITIONS

CIOMS Reportable Case Histories (CIOMS Reports)

Serious, medically substantiated, unlabeled adverse drug reactions about which there is sufficient information. Four pieces of information constitute a minimum report: an identifiable source of the information, a patient (even if not precisely identified by name and date of birth), a suspect drug, and a suspect reaction.

Core Data Sheet (International Prescribing Information)

A document prepared by the pharmaceutical manufacturer, containing all relevant safety information, such as adverse drug reactions, which the manufacturer stipulates should be listed for the drug in all countries where the drug is marketed. It is the reference document by which "labeled" and "unlabeled" are determined and is therefore always included in a report.

Data Lock-Point (Cut-off Date)

The date designated as the cut-off date for data to be incorporated into a particular safety update. On this date the data available to the author of the safety report are extracted for review and stored.

International Birth Date

The date on which the first regulatory authority to approve a particular drug for marketing has done so. The proposal is that the manufacturer's data are extracted for review of the particular drug every six months subsequently, and that all regulatory authorities that wish to have safety updates will accept the same cut-off date.

International Prescribing Information

See Core Data Sheet

Serious

Fatal, life-threatening, involved or prolonged inpatient hospitalization, or resulted in persistent or significant disability or incapacity. These are the four categories specified on the "CIOMS Form" designed by the CIOMS Working Group for reporting of serious adverse drug reactions (CIOMS Working Group I). CIOMS safety updates require consideration of all drug interactions, cases of drug abuse, and cases of significant overdosage; therefore these cases could also be considered "serious" and included in line listings in CIOMS safety updates or added as a separate table.

THE PROPOSALS

Approach Taken

The safety updates addressed by CIOMS Working Party II are routine compilations needed so that manufacturers and regulators can be reassured that pertinent safety data available to the manufacturers are systematically reviewed. The proposals should be viewed as the core package of information which should be included in any periodic report. The goal of standardizing these updates is to assist doctors and scientists responsible for monitoring drug safety in industry to focus on reviewing the data and to assist inter-regulatory communication, and not simply on generating a battery of different reports.

CIOMS working parties do not draft regulations — it would be inappropriate for them to try to do so, but to call their consensus views "suggestions" would be to undervalue the quality of the decisions reached. They therefore formulate proposals. These proposals describe the meaningful medical safety information which should be periodically reviewed and summarized in order to reassure the regulator and the regulated that the safety profile of the drug has not changed significantly since the time of the prior review, or, if it has, to provide suitable documentation.

Unlike the focus of the CIOMS I expedited reports scheme on foreign case histories, there was agreement that the periodic safety-update should include all appropriate reports — foreign or domestic.

The areas covered in the proposals are:

Scope

I Subject drugs for review.
II Frequency of review and reporting.

Content

I Introduction.
II Core data sheet.
III The drug's licensed status.
IV Review of regulatory actions (if any).
V Patient exposure.
VI Individual case histories.
VII Studies.
VIII Overall safety evaluation.
IX Important data received after data lock-point.

Scope

I. Subject drugs for review

The proposal was that summary updates in the proposed format should be prepared for all new Chemical entities licensed for the first time during 1992

and thereafter. Subsequent updates would include data for a specified six-month review period (interval). Cumulative data are only provided to place issues in perspective, in particular a drug's licensed status. The value of periodic safety updates decreases for older drugs.

Summaries should include combination products, with reference to the active moiety. It will often be appropriate in a given report to separate different formulations, routes of administration, and indications (if this information is available).

When relevant, the safety update could also differentiate data associated with salient pharmaceutical facts, including the active moiety or moieties, excipents, strength(s) and dosage form(s), ete.

II. Frequency of review

Each subject drug will have an international birth date, which will be the date on which the first regulatory authority approved the drug. The manufacturers' data base will be frozen for each particular drug every six months subsequently.

Thus all drugs will have specific "official" data lock-points (DLP), at six-monthly intervals. The implication of this is that, irrespective of date of approval, all regulators requesting or expecting to receive CIOMS periodic reports will receive them within the first six months after the drug's approval in their countries, and then subsequently at six-monthly intervals. Normally the manufacturer would make each report available within 45 calendar days of the DLP.

The Working Group decided that it would not be helpful to adopt a rigid periodicity of reporting. The consensus favoured an initial six-monthly periodicity of review, with six-monthly updates. While it was understood that not all regulatory authorities would require these updates every six months, the Group recommended that the cumulative series of such six-monthly updates would suffice to fulfil the needs of any regulators requiring yearly, two-yearly or five-yearly updates.

Also unanimously agreed was the need to include or otherwise submit more up-to-date medical safety data (data that become known to the manufacturer only after the drug's DLP and that might influence the evaluation). It is worth re-emphasizing that urgent data must also be reported separately from the safety updates.

Content

I Introduction

The introduction should follow the reports title page and table of contents. The manufacturer should briefly introduce the drug so that the report "stands alone" and the reviewer cannot misinterpret the scope of the report. Reference should be made to not only product(s) covered by the report but also those excluded because, for example, they are covered in another manufac-

turer's or in a separate moiety report. Data from co-marketers or licensees should be included unless it is known that they are submitting their own safety updates.

II Core data sheet

The core data sheet (see definition, page 12) must be included for reference in the report.

III The drug's licensed status for marketing

Brief information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has ever been made (e.g. approved, approved with qualifications, rejected, etc.). This should be presented in order of date of approval. Submissions voluntarily withdrawn by a manufacturer before a regulatory decision is taken, for reasons other than safety (e.g. commercial considerations), need not be included, but if the submission is withdrawn for safety reasons the information must be included.

Besides listing the dates of approval (or rejection) the date of market introduction (launch date) should also be given. The table could also usefully give the "trade names" in the different countries where the drug has been launched. Approved indications for use may differ among countries, and details should be provided if they are relevant to interpretation of clinical safety information. This section (Section III) of the report is the only one that is cumulative.

IV Update of regulatory or manufacturer actions taken for safety reason

An update on the significant regulator-initiated or manufacturer-initiated actions taken, or to be taken, for safety reasons during the report period anywhere in the world should be presented. This would include: drug suspension; restrictions on distribution; any curtailment of trial programmes; significant alterations to label/package insert such as new contraindications, warnings or addition of important adverse drug reactions; lowering of recommended dosage; pharmaceutical changes, e.g. change of excipients, for safety reasons.

The format should be a brief narrative stating the reasons for significant regulatory or manufacturer action, with documentation appended when appropriate.

V Patient exposure

Any safety update must address interim patient exposure (sales experience) matching as far as possible the period covered by the interim safety data, in order to place these in general perspective. When a pattern of ADR reports indicates a potential problem, detailed utilization data should be supplied if appropriate. Ideally these data would include the number of prescriptions

or patients exposed, but up-to-date information by country is not usually available.

The estimated patient-months of exposure (e.g. patient packs) is also sometimes difficult to calculate, especially when there may be several recommended dose regimens. Where these preferred figures cannot be estimated by the manufacturer, a proposal was that tonnage of sales be given by country, where possible. An option could be as a tabulation. The recommended daily doses should be stated.

The method used by the manufacturer to estimate patient exposure should always be outlined.

VI Individual case histories

The appropriate individual case histories defined below should be included only if received during the six-month period of review. All should be presented in body system order, in the CIOMS line-listing format described in (e) below and summarized in Annex 5.

a) Relevant individual case reports from studies (published or unpublished)

These should be the unlabeled, serious cases (including interactions, abuse and overdosage) that are considered attributable to the drug by *either* the manufacturer *or* the investigator. What is or is not "labeled" for a drug should be based on the International 'Core' Data Sheet or prescribing information (see definition) or, where appropriate, the Investigators Brochure.

b) Spontaneous reports

All individual case reports sent spontaneously to the manufacturer and attributed to the drug which are serious (including interactions, abuse and overdosage), irrespective of labeling, or non-serious unlabeled, should be submitted. Consumer reports that cannot be medically confirmed should be included if considered relevant by a medical professional in the industry. The manufacturer should make every effort to have all reports medically confirmed. Spontaneous reports on the drug prescribed generically should be included when the manufacturer is unknown.

c) Published individual case histories

Similarly, the manufacturer should include all published reports of ADRs that are serious, irrespective of labeling, or non-serious, unexpected, known to the manufacturer, where the review drug is specifically suspected as being causally related. Reports in the lay press are excluded.

d) Serious case reports from other sources

Manufacturers sometimes receive ADR information on individual patients from other sources, including regulatory authorities; these need not be listed.

A manufacturer may receive reports on products licensed to or from other manufacturers, and, if another manufacturer is known to be reporting them, such secondary reports need not be included in the CIOMS line listing. A signal generated on the basis of these case reports should be reported in the narrative with sufficient case information. The aim is to be comprehensive but to avoid duplication of reporting.

e) CIOMS line listing

All the required individual case reports specified above should be presented by body system in the format of a CIOMS line listing (see Annex 5). Ideally, there should be one listing, but separate listings might be made, for example, for different formulations, indications, or routes of administration. The source of the case history (e.g., trial, physician, other health care professional, publication) should always be given. Each patient should appear only once in the CIOMS line listing, under the most serious condition. However, where considered useful, a method of body system cross-referencing (or even a supplementary tabulation) can be used if a patient has a group of different reactions that would normally be classified in separate body groups. Where appropriate, a secondary sub-grouping, by country, is also desirable.

The CIOMS line listing should include cases that qualified for reporting as CIOMS reports (CIOMS Working Group I). If considered helpful, these cases could be identified (e.g., asterisked) in the line listing. For published individual case histories, the literature reference should be given as a footnote.

A "Comment" column could usefully be added to the CIOMS line listing. The manufacturer could use it to highlight important factors such as date of the reaction, importance of the underlying disease, or unrelated outcome, e.g., death from other causes. It could be used also for the causality assessments of French spontaneous reports prepared for the French regulatory authority.

f) Narrative review of the individual case histories

The report could include a brief narrative based on the manufacturer's analysis of the cases presented in the CIOMS line listing (including a comment on increase in frequency).

VII Studies

These should include only relevant studies, as follows:

a) Newly analysed studies containing important safety information

There should be a listing of all relevant studies (non-clinical, clinical, and epidemiological) newly analysed during the update period and containing important safety information. Toxicological studies and laboratory data would be included if they contain important relevant safety data. Copies of any reports will be provided only when deemed appropriate.

b) Targeted new safety studies (either initiated during the period of review or continuing)

New studies specifically set up to examine a safety issue (actual or hypothetical), initiated or continuing during the period, should be described (scientific objective, starting date, number of subjects, protocol abstract, etc.). When analysed, the results of these safety studies should be summarized as in a).

c) Published safety studies

The report should include new important safety findings (positive or negative) found on review of published toxicological, clinical and epidemiological studies. It should include published abstracts from important relevant meetings.

A brief narrative overview with a bibliography of published material reviewed could be attached.

VIII Overall safety evaluation

The safety update should include a concise critical analysis and opinion written in English by a person responsible for monitoring and assessing drug safety. Any new important information on the following should be explicitly included:

i) increased frequency of known toxicity

ii) drug interactions

iii) overdose and its treatment

iv) drug abuse

v) positive and negative experiences during pregnancy or lactation

vi) effects of long-term treatment

vii) any specific safety issues relating to the treatment of special patient groups, such as the elderly or the very young.

For each of these points, lack of significant new information should be reported.

The evaluation should indicate in particular whether the interim safety data remain in line with the cumulative experience to date and the manufacturer core prescribing information (appended), and should specify any action recommended and the reasons why.

IX Important information received after data lock-point

This section is for reporting any important new information received by the manufacturer since the data base was frozen for review. It may include significant new cases or follow-up data that affect the interpretation or evaluation of existing reports.

Annex 1:
Membership of CIOMS Working Group II

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The success of CIOMS Working Group I had been due mainly to the following factors: the limited number of participants from both regulators and industry, their dedication, the clearly specified scope of the task, the neutral platform provided by CIOMS, the recognition of the importance of the task and the readiness of all to seek pragmatic Solutions for the sake of standardization, even if such Solutions did not correspond exactly to their current procedures. It was a working party and not a debating society. The members of the group had committed themselves to the immediate implementation of the proposals as a pilot project, and the representatives of industry to communicating the proposals to local manufacturers.

As some companies and regulatory authorities had indicated some dissatisfaction at not being represented in Working Group I, the co-chairpersons of Working Group II increased the representation of both manufacturers and regulatory bodies, though recognizing the risk in doing so of reducing the efficiency of the work. To compensate for the still necessarily limited membership, the members were encouraged to have discussions outside the group to broaden the base of the conceptual and practical issues covered, and in recognition of the complexity of the issues involved in safety updating.

A prerequisite for industry membership of CIOMS Working Group II was willingness to implement any agreed procedures initially as a pilot project. One of the roles of the regulators represented was to review the usefulness of the examples generated by industry members, based on the new proposals and agreed set of definitions, format and content, so as to avoid any undue increase in regulatory requirements.

Annex 2:
Meetings of CIOMS Working Group II

Annex 2: Meetings of CIOMS Working Group II

At the first meeting (Amsterdam, October 1989) the members, häving agreed upon the aims, divided into two groups, one on safety data, and the other on the drugs, the timing of reports, and incorporation of other information — e.g. about regulatory actions in relation to the drug worldwide.

At the second meeting (Zürich, April 1990) the group reviewed all the earlier proposals as a whole. Subsequently Dr Win Castle prepared a very preliminary draft final report.

At the third meeting (San Francisco, June 1990) a small group who were attending the DIA annual general meeting reviewed the draft report and agreed that after the October 1990 meeting all the representatives from industry should be prepared to implement the proposals decided there, as a pilot demonstration project, for at least one drug. These proposals would then be again reviewed and discussed before going further.

At the fourth meeting (Amsterdam, October 1990) the project moved into the pilot phase and the objectives and methods of assessment to be used were agreed, largely on the basis of the initiative of Dr Hugh Tilson (see Annex 3).

At the fifth meeting (Milan, May 1991), on the basis of the results of the ten manufacturers' prototypes (see Annex 4), the proposals for periodic safety updates were clarified, refined and agreed. A draft final report was prepared describing the proposals, and a mock-up prototype was included.

At a final meeting (Basel, September 1991) the final recommendations were unanimously agreed and the present report adopted. Regulatory members of the Working Group undertook to try to modify their reporting requirements to take into account as many of these standard recommendations as possible; to the same end, copies of this report would be widely disseminated to responsible industry associations.

Reaching Consensus: Debate and Decision

From the beginning, representatives of both sides acknowledged the need for compromise on controversial issues relating to both the scope and the detailed substance of a well-crafted and useful periodic safety update (PSU) report. The also realized that they represented a relatively small proportion of the world's many regulatory bodies and manufacturers concerned with this topic, and whose ideas and perspectives on the matter might differ from theirs.

Therefore, the reader is assured that, during about 75 hours of meetings on six occasions (and through correspondence) between October 1989 and September 1991, some 20 members of CIOMS Working Group II engaged in extensive and usually heated — but always constructive — debate covered the widest breadth and spirit of the group's deliberations. To indicate how the contents of the present proposal were decided, highlights are presented below of: (1) discussions held on key, specific issues, (2) the experiences and lessons gained by both manufacturer and regulator from the 10 pilot (prototype) reports (see Annexes 3 and 4), and (3) unresolved issues or controversies that need ongoing debate.

1. Debates on key issues

In separate and joint early discussions, the regulatory and manufacturer groups arrived at complete agreement on what general areas should be covered in a periodic safety report, applying criteria of relevance and importance from a public health perspective, and of what information a small or a large company should be reasonably expected to obtain and assess routinely: worldwide marketing license status, significant actions (labeling, etc.) taken or imposed related to safety, some measure of patient drug use (exposure), summary of certain types of individual cases of ADR, information from clinical or preclinical studies relevant to important safety findings, and overall evaluation by a qualified person. Within these broad areas, it was the specifies on definitions, inclusion and exclusion criteria, levels of detail needed, and logistics of preparing and disseminating a standard report that led to extensive debate and eventual compromise. Ultimately, a set of guidelines resulted, establishing basic, minimum standards; as usual, additional types and amounts of data can be included if indicated by circumstances. Some representative examples will illustrate the innumerable questions and options raised in dealing with specific items.

- *What is the appropriate periodicity for a report?*

How often can and should a company review its data base for a product on the market in one or more countries? Since urgent matters are handled through *ad hoc* alert mechanisms, why not yearly or every two years, as some (including regulators) suggested for the more routine information in a PSU? Once the data base cut-off is declared, what is a reasonable time in which to prepare and disseminate a PSU to ensure that the information is not outdated?

It was decided that six-monthly data lock-points and a 45-day preparation period were practical and useful, especially since introduction of products and subsequent experience gained in diverse markets are usually spread over several years.

- *What should the anniversary reporting date be?*

The principles governing the decision were: manufacturers should prepare the update summary once and provide the same information to all interested parties (regulators) at the same time. Thus, establishing an international birthdate (date of first approval anywhere) was acceptable and is not expected to compromise current practices in countries requiring periodic safety updates.

- *What clinical safety data should be included and how should they be presented?*

Should the reports cover the six-month interval or be cumulative? Should they include all worldwide spontaneous reports received by the manufac-

turer, independent of source (physician, patient, regulator, literature, other) or nature (serious, non-serious, labeled, unlabeled, etc.)? Should detailed case histories or summary listings be presented? Should all or selected safety data from clinical studies be included? Should the data originate from completed and analysed studies or should results from continuing studies also be included? Should any attention be given to new preclinical safety information?

As expected, these and many more questions in this area involved the most intense debate of all. The compromises reached and the proposals are embodied in Sections V and VI of the report (p.p. 15-17). It should be emphasized that the proposed standard material can be supplemented if appropriate. It was agreed that the principles previously developed and implemented for the CIOMS Working Group I system on alert reporting should be retained for the corresponding information in a PSU report. It is of interest to note that a detailed assessment of the use and experience with the CIOMS alert reporting procedure is under way by Dr. W. Castle; results are expected early in 1992.

• *How is an unexpected (unlabeled) adverse reaction defined?*

For a marketed product, it was deemed reasonable that a manufacturer should develop a "core data sheet" (may also be referred to, for example, as the core — or company — product document or package insert) containing all safety information (under warnings, precautions, adverse effects, ete.) which the company stipulates should be listed for the drug in all countries where the drug is marketed.

Countries often differ in their safety-labeling practices, for local reasons. However, to avoid the difficulty and confusion that would be associated with customizing "expectedness" for individual countries, it was agreed that the manufacturer's Central (core) labeling document should serve as the standard for a PSU report.

2. The experience of the pilot project

The 10 participating manufacturers used the criteria for a PSU report established during the first year of the Working Group's activities to prepare and evaluate, as a pilot project, a sample report on a product of their choosing. Many lessons were learned from this experience and its review with respect to: availability of information within a company, clarification of the guidelines themselves, the significance or relevance of the various data components, and the practical implications of compiling and reviewing such reports. The experience led the group to challenge some previous assumptions and decisions. The refinements and changes resulting from this experience were predicated on the notion that a PSU should contain sufficient information to assure regulators that manufacturers regularly gather and review relevant data. At the same time, the PSU should be as brief as possible. The same information should enable the regulators to fulfill their public health role

in monitoring product safety. The group regards the final proposal as a practical, achievable, standardized means of meeting these goals.

3. Unresolved issues for continuing discussion

Several issues arose that were outside the scope of the group's objectives, but which affect several aspects of the proposed PSU summary. They are mentioned here to increase recognition of the problems and to stimulate wider discussion. Some might even serve as the basis of a later CIOMS Working Group.

- What standards should be used for assessing increased frequency of known (labeled), especially serious, adverse events?
- Is it feasible to establish international standard clinical definitions and specifications for the elements of a core data sheet, at least with regard to safety?
- Could or should the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden) serve as the Central source for worldwide data on spontaneous adverse reactions? Would this permit more convenient access to the different regulatory reaction "registries"? Many adverse reactions of particular interest are reported direct to regulators and not to manufacturers.
- Although the present proposal calls for implementing the suggested PSU format for drugs introduced for the first time from the beginning of 1992, what about new combinations or dosage forms introduced after 1991 but involving one or more drugs already on the market? Also, is it feasible (for manufacturers) to use the same format for all currently marketed Products?
- When does a product become so "old" that a PSU report becomes unnecessary or could be prepared less frequently?
- Is it possible to foster the development of better resources and methods for estimating patient exposure?

Annex 3:
The Pilot Phase and Criteria/ Strategies for its Evaluation

Annex 3: The Pilot Phase and its Evaluation

Manufacturer representatives had undertaken as a prerequisite of membership of Working Group II to implement agreed procedures as a pilot project, in order to assess the feasibility and utility of a single international periodic safety-update summary report. Each manufacturer representative undertook to draft a single prototype summary-report on an actual drug, and to send a copy to each regulatory member of the group. These were sent directly to each regulatory member by name (i.e. unofficially). Each page was to be marked "confidential". To avoid any undue increase in regulatory requirements, regulator representatives reviewed the usefulness of the examples of safety-update reports drawn up by the manufacturer representatives on the basis of the new proposals and the agreed definitions, format and content. All the regulators reviewed all the prototypes (even if the drug had not been approved).

Also, each manufacturer submitted a "sanitized" (modified so as to divulge no proprietary information) prototype report to the other manufacturer members.

All members of the Working Group took part in the critical evaluation of each pilot document. The criteria for evaluation referred to data availability to manufacturers (did a company have easy and systematic access to the necessary data; if not, why?); the resources in time and money needed to produce or review the update; ease of array and automation needs and costs — whether it was possible to produce the update tables by Computer, and how easy it would be to make programming changes; technical difficulties in determining the data lock-point (DLP) or in obtaining the necessary data before the DLP; level of detail desirable or possible in the information; time taken to produce the update and how long it should take (for one or several products); and time taken by English-speaking and non-English-speaking regulators to review the update.

Utility was evaluated against criteria of acceptability and informativeness of data, and whether the data met existing regulatory standards; quality (in comparison with update summaries normally received); information content; timeliness (up to date or out of date); clarity of language, ease of comprehension; compatibility with other (e.g., two-yearly) reports; and applicability to IND safety or pre-approval reporting requirements.

The pilot phase

Purpose

- A field test to assess feasibility and utility of a single international interval safety-summary report (six-month lock-point).

Process

- each manufacturer (as a condition of future participation in the CIOMS Working Group) must draft a single prototype summary report on a real drug.
- the report must be sent directly but unofficially to each regulatory member. Each page will be marked confidential.
- all the regulators will review all the prototypes (even if the drug has not been approved).
- each manufacturer will also submit a "sanitized" prototype to the other manufacturer members i.e. no proprietary information divulged. Each page will be marked confidential.
- all members of the Working Group participating in the pilot phase will participate in the critique process (see next page).

Product
- revised document and a model report.

Time-line
- manufacturer prototype as soon as possible, and not later than March/April 91.
- Group discussion of progress in May 91.
- Group review/final report by October 91.

Content
- One brief report — a "real" one "sanitized" for the manufacturer group.
- Interim (six-month period).
- may be retrospective or prospective.
- recent drug.
- worldwide scope (highlight problems in generating report).
- standard outlines/elements.

Criteria/strategies for evaluating the pilot phase

Feasibility
- Data availability — did the company have easy and systematic access to the types of data to be incorporated? If not, what difficulties were encountered?

Resources
- How much resource time and money did it take to produce or review the update?
- Ease of array/automation needs and costs — was it technically feasible to generate the update tables by Computer? How easy would it be to make programming changes?
- Logistics of data lock-point — were there technical difficulties in determining the DLP or accessing data within the DLP?
- Specificity vs aggregation — how detailed should or can the information be?
- How long did it take to produce the update? How lõng should it take? For one or several products?
- Regulator review time — how long did (I) English-speaking (II) non-English-speaking regulators take to review the document?

Utility
- The data ("Acceptability and informability") — Do the data meet current regulatory standards and are they informative?
- Quality — is the pilot update as good as, or better than, the update that the regulators now receive?
- Information content —- does it generate the right questions (and the wrong questions)? Have we learned anything new about the drug?
- Timeliness — are the data presented in the pilot update current enough or are they out of date?
- Clarity — is it user-friendly? Are there language issues?
- Comparability — is it compatible with other periodic reports (e.g. 2 years)?
- Applicability — could this report be used to meet some IND safety reporting requirements or pre-approval reporting requirements?

Annex 4:
The Pilot Phase:
Companies Submitting Prototypes

Annex 4: The Pilot Phase: Companies Submitting Prototypes of Periodic Safety Summaries

1.	Burroughs Wellcome	Semprex* (acrivastine)
2.	Ciba-Geigy	Trileptal (oxcarbazepine)
3.	Glaxo	Zofran (ondansetron)
4.	Hoechst	Tritace (ramipril)
5.	Hoffmann-La Roche	Anexate (flumazenil)
6.	Jouveinal	Debridat (trimebutine)
7.	Lilly	Vancocin (vancomycin)
8.	Merck Sharp & Dohme	Pepcid (famotidine)
9.	Pfizer	Cardura (doxazosin)
10.	Roussel Uclaf	Rulid (roxithromycin)

* Also Exosurf.

Annex 5:
CIOMS Standardized Line Listing of Adverse Drug Reactions

Annex 5: CIOMS Standardized Line Listing of Adverse Drug Reactions*

Presented in body system order for the most serious presenting sign or symptom:

COLUMNS:

Country

Source e.g. trialist, physician, literature

Age

Sex

Dose of the drug

Duration of treatment (prior to event); time to onset

Description of reaction (as reported)

Outcome e.g. fatal, resolved

(Comment)

Company reference number

* WHO codes could be used for some items.

Annex 6:
Fictitious Example of Periodic Safety Update

CONFIDENTIAL

International Drug Surveillance Department

Andson Research Limited

ARDS91/023

QWEASYTROL: SAFETY UPDATE

01 October 1990 to 31 March 1991

Number of pages: 29

Copy number

Distribution:

TABLE OF CONTENTS

APPENDICES

Introduction

This report is the fifth of the series of safety updates on qweasytrol compiled for regulatory authorities in the format proposed by CIOMS Working Group II. It summarizes the safety data received by the International Drug Surveillance Department at Andson Research Ltd., from worldwide sources, between 01 October 1990 and 31 March 1991. For cumulative experience the reader is referred to previous qweasytrol safety updates (ARDS89/032, ARDS89/063, ARDS90/028 and ARDS90/072).

Qweasytrol is a highly selective epsilon-G_2 receptor antagonist first approved for marketing in the UK in October 1988. It is indicated for the symptomatic treatment of nausea and vertigo due to Menieres disease and other labyrinthine disturbances, and for the prevention of motion sickness. It is also effective in the treatment of nausea and vomiting associated with gastrointestinal disorders, cyclical vomiting, congestive heart failure and post-anaesthetic vomiting. It has been approved in South Africa for the prophylaxis of acute neurological attacks in patients with porphyria variegata. High doses, 400 mg daily, are required for this indication and its use is reserved for patients with frequent severely disabling attacks. Qweasytrol is undergoing clinical trials in the management of nausea and vomiting associated with cytotoxic chemotherapy.

Qweasytrol is available for intravenous injection and as tablets and suppositories. Safety data for all formulations have been included in this update. Qweasytrol has also been licensed in some countries in combination with sedazepam, as co-sedqweasytrol. A separate safety update for this formulation will be produced in August 1991 when sedazepam is reviewed.

2. Core Data Sheet

The core data sheet for qweasytrol is presented in Appendix 1.

3. Licensed Status

Qweasytrol has been approved for the treatment of nausea and vomiting in 12 countries and until 1 March 1991 was launched in 11 (see Appendix 2). In addition, it has been approved and marketed in South Africa for prophylaxis of porphyria variegata.

In Denmark it was approved with the qualification that it should not be administered to elderly patients as it was considered that there were insufficient data to assess its safety in this population.

Submission was rejected in Venezuela because some patients in clinical trials in Menieres disease had experienced blurred vision.

4. Update on Regulatory or Manufacturer Actions Taken for Safety Reasons

During the six-month period of this review there have been no new license application rejections for safety reasons, drug suspensions, or restrictions to distribution. However, pre-marketing clinical trials in which high doses of qweasytrol have been administered intravenously for the treatment of

chemotherapy-induced emesis have been discontinued after reports that two patients receiving intravenous bolus doses of qweasytrol, 6 mg, experienced temporary blindness. Other intravenous studies have been suspended.

The data sheet for qweasytrol has been amended to contraindicate its use in patients who have received monoamine oxidase inhibitors within the previous 14 days. This followed the results of in-house interaction studies which demonstrated the potential for severe hypertensive crises.

Qweasytrol tablets 25 mg have been reformulated with the exclusion of the azo dye, sunset yellow, after early reports of hyperactivity in some patients.

5. Patient Exposure

5.7 *Clinical trials*

From patient-record books returned to the manufacturer, it is estimated that 350 patients received qweasytrol by intravenous injection for the treatment of chemotherapy-induced emesis during the period of review, 01 October 1990 to 31 March 1991. No other clinical trials were in progress during this time.

5.2 Market experience

A rude estimate of the number of patients treated with qweasytrol during the period of this safety update has been calculated from the sales volumes, in kg, of raw drug sold in the period 01 September 1990 to 28 February 1991. More recent sales data are unavailable. Apart from the South African data, which have been calculated separately, it has been assumed that each patient has received a standard dose of 30 mg daily and has continued treatment for the entire 26 weeks. Clearly, this underestimates the number of patients exposed to the drug.

In South Africa, where the only licensed indication is in prophylaxis of porphyria variegata, a standard dose of 400 mg daily for 26 weeks has been assumed.

Sales volumes 01 September 1990-28 February 1991

1. Worldwide (exeluding South Africa)

Assuming dose 30 mg daily for 26 weeks:	
kg soid	2,560
cumulative dose per patient (g)	5.46
number of patients treated	468,860

2. South Africa

Assuming dose 400 mg daily for 26 weeks:	
kg soid	72.0
cumulative dose per patient (g)	72.8
number of patients treated	989

5.3 Total exposure

Clinical trials	350
Worldwide sales (excluding South Africa)	468,860
South African sales	989
TOTAL	470,199

Thus it is estimated that over 470,000 patients received qweasytrol in the period covered by this safety update.

6. Individual Case Histories and OverView

All spontaneous and clinical-trial reports, published and unpublished, meeting the criteria defined below and received by the International Drug Surveillance Department, Andson Research Ltd., from worldwide sources, between 01 October 1990 and 31 March 1991, are presented in Appendix 3. The cases have been arranged by body system and the details tabulated in the CIOMS line-listing format. Where reports of events affecting more than one body system have been received, the most clinically serious event has been assigned to the corresponding body system and the other events listed with it. However, it has been considered appropriate to cross-reference some multi-system events.

Spontaneous reports: All serious (irrespective of labeling), and non-serious unlabeled, spontaneous reports received by Andson Research Ltd. and its licensees both by trade name and generically, with the exception of those notified directly by regulatory authorities, and medically unsubstantiated consumer reports that are not considered to be medically significant. Qweasytrol is not manufactured or distributed by any other source.

Clinical trial reports: Unlabeled, serious attributable adverse event reports. An unlabeled event is defined as any particular untoward medical happening experienced by a patient which is not described in the core data sheet. A serious event is one that is fatal, life-threatening, disabling, incapacitating, results in hospitalization or prolongs hospitalization, overdose, cancer or a congenital anomaly. For the purpose of this report an event has been considered to be attributable if the investigator has rated the causality relationship with qweasytrol as possible or greater.

All cases reported individually on an expedited basis to regulatory authorities because they fulfilled CIOMS Working Group I criteria have been marked with an asterisk beside the company reference number.

OverView

A total of 43 reports fulfilled the criteria for inclusion in this safety update. Of these, 37 were spontaneous reports, including three cases of eataraet noted in a survey published in the literature (Ref. 1, Appendix 5), and one case of severely disabling blurred vision in a glaueoma patient participating in a qweasytrol

post-marketing surveillance study. Ten reports fulfilled the CIOMS Working Group I criteria for individual reporting.

An analysis of all reports received during the six-month period of review indicates that the majority are either of side-effects already included in the current core data sheet or of isolated cases for which there is often a more probable alternative cause. The remaining cases have been reviewed against all cumulative experience to date and three areas of interest have been identified: eye disorders (in particular blurred vision and cataract), alopecia and thrombocytopenia. Eye disorders and thrombocytopenia will be discussed more fully in the overall safety summary (see sections 8.1 and 8.2 below).

Alopecia was discussed in a previous safety update (ARDS89/063). Despite the receipt of the four cases presented in this report and a further two cases received from the UK regulatory authorities in this period, it is still considered that the reports reflect a common occurrence in the population of patients treated with qweasytrol, rather than a drug-related effect.

7. Studies

7.1 Newly analysed studies

Of the studies analysed during the update period only one produced new potentially important safety data; details are tabulated in Appendix 4. This study was discontinued after only 29 of the intended 50 patients had been entered, because of the onset of temporary blindness in two patients receiving intravenous bolus injections of qweasytrol, 6 mg. Details of these two cases were given in the previous safety update (ARDS90/072). All other studies using bolus intravenous doses have been discontinued; those using slow intravenous infusions have been suspended.

7.2 Targeted new safety studies

Animal studies, as described in the previous update (ARDS90/072), are continuing in order to determine the aetiology of the temporary blindness in two patients receiving high-dose rapid intravenous bolus injections of qweasytrol in a dose-ranging study in cisplatin-induced emesis. No positive results have been found to date.

An epidemiological study is to be undertaken to investigate further the association between qweasytrol and cataract formation described by Aucoma and Opia (Ref. 1, Appendix 5). Using the Hospital and Drug Care record linkage data base, it is proposed to identify all patients in the UK who have been hospitalized for cataract extraction between 01 January 1989 and 31 December 1990, by decade of life, and to further determine the number who have received at least two prescriptions for qweasytrol since its launch in October 1988. Further details of the protocol will be submitted in the next safety update.

7.3 Published safety studies

There have been three publications during the update period, which describe potential important new safety information. The bibliography is listed in Appendix 5.

In an abstract presented at the 7th International Congress of Neuroptometrists, Lada et ai presented data to demonstrate that qweasytrol had significantly less effect on reaction time in healthy volunteers than either promethazine or cinnarizine (Ref. 2, Appendix 5). They concluded that qweasytrol was probably the drug of choice in patients requiring treatment for motion sickness who then needed to drive. There is a statement in the current data sheet warning that patients should not drive or operate machinery if drowsiness is experienced.

During chronic-toxicity testing of large doses of qweasytrol in rats, oedema and pulmonary fibrosis were noted in three of 20 male rats treated and then sacrificed after six months (Ref. 3, Appendix 5). There were no similar findings in toxicity testing previously undertaken by Andson Research Ltd. The clinical significance of this finding is unknown. There has been one previous spontaneous report of a patient who had received large doses of qweasytrol for three months for porphyria prophylaxis and who then developed pulmonary oedema (see ARDS90/072).

The final publication was a pharmacoepidemiological study undertaken with the computerized registry of drug-induced ophthalmic disorders at the University of Cataractus, USA (Ref. 1, Appendix 5). Interrogation of the data base had demonstrated a significantly higher risk of subcapsular cataracts in patients receiving epsilon G_2-receptor antagonists. Details were given for three patients who had received qweasytrol, and these are included as spontaneous reports in Appendix 3.

8. Overall Safety Evaluation

From the data presented in this safety update and cumulative experience to date it is considered that no further amendments to the core data sheet are required at present. However, there are two areas for continued close monitoring: visual disorders and thrombocytopenia.

8.1 Visual disorders

During the period of review nine reports of visual disorders were identified for inclusion in the safety update — five cases of blurred or double vision, three reports of cataract, and one report of conjunctivitis.

Blurred vision was reported in pre-marketing clinical trials but the incidence was similar to that seen with both placebo and comparators. Since marketing there have been other isolated spontaneous reports of blurred vision, but either there have been alternative explanations for the symptoms or the cases have been poorly documented. Of the five cases presented in this report there is dechallenge information for only three. In one the symptoms improved and in the other two they persisted. However, in one patient this was due to an acute exacerbation of glaucoma. On the remaining two cases further details

are still awaited but the reports of blurred vision were considered to be of less clinical importance than the principal events being reported, namely renal failure and thrombocytopenia.

The three reports of cataract originated from a publication by Aucoma and Opia (This is presented in Appendix 6.) The authors identified an increase in the incidence of subcapsular cataracts in patients receiving all epsilon G_2-receptor antagonists, including qweasytrol. These data had been collected over several years. It is of note that the patients were aged 69-84 years and that cataract is common in this age group. It is estimated that the rate of admission to hospital in the UK for cataract extraction in patients aged 65 years and above is three per 10^3 (personal communication — Hospital and Drug Care record linkage data base). There is no evidence that there would be any significant difference in Southern States, USA. Further clinical details on these three cases have been requested through our USA subsidiary.

Since marketing, there have been four other reports of cataracts, from worldwide sources, all occurring in patients over 65 years. The significance of these cases is unknown at present and the results of the epidemiology study described in Section 7.2 are awaited.

As discussed in the previous safety update, temporary blindness has been associated with only the rapid intravenous administration of high doses of qweasytrol in chemotherapy-induced emesis, and would not be expeeted to occur in patients receiving the recommended intravenous dose for licensed indications. However, if any further reports are received Andson Research Ltd. would consider sending out a “Dear Doctor” letter to warn prescribers of the possible hazards; an appropriate statement would also be added to the core data sheet.

8.2 Thrombocytopenia

Three cases of thrombocytopenia have been reported in this safety update. Two were in patients in clinical trials receiving qweasytrol for the control of vomiting after cytotoxic therapy for non-Hodgkin’s lymphoma. The platelet nadirs occurred 10 days after the administration of chemotherapy at eight and five days after qweasytrol had been discontinued. The reporting investigator considered that qweasytrol possibly contributed to the dramatic platelet falls. Neither patient had previously received courses of cytotoxic therapy or qweasytrol. The other case occurred in a patient receiving qweasytrol for Menieres disease.

About six weeks after commencing therapy epistaxis and extensive bruising began. The platelet count was below $10x10^9$/l and the patient was admitted to hospital for platelet transfusion and further investigation. Further clinical details are awaited.

There have been previous isolated reports of thrombocytopenia in patients receiving qweasytrol but most have occurred in clinical trials where cytotoxic therapy is administered concurrently. However, potentiation of the myelotoxic effects of cytotoxic therapy cannot be excluded.

There are three other spontaneous reports in patients receiving treatment for Menieres disease. One patient had a previous history of spontaneous idiopathic thrombocytopenia and in the other two cases the time to onset was consistent with a co-trimoxazole-related causality.

8.3 Increased frequency of reports

Apart from the three cases of cataract originating from the same publication and reports of blurred and double vision, there is no evidence of a significant increase in the frequency of any event reported during the period of review compared with the previous six-month update.

8.4 Drug interactions

A statement has been added to the data sheet contraindicating the use of qweasytrol in patients who have received monoamine oxidase inhibitors in the previous two weeks, because there is now evidence that this may result in a severe hypertensive crisis (see ARDS90/072).

Apart from an additive sedative effect with hypnotics, anxiolytics and alcohol, no other drug interactions are known but no formal studies have been undertaken. Specifically, there have been no spontaneous or clinical trial reports of drug interactions. However, there have been individual cases of enhanced myelosuppression when administered with cytotoxic agents as described above.

8.5 Overdose

There have been no new reports of overdose during the period of this update. There are only four cases known to the company, all of which responded to conservative treatment.

8.6 Abuse

Although there have been isolated reports of transient euphoria in patients commencing treatment with high-dose qweasytrol for prophylaxis in porphyria, there is no evidence of abuse potential.

8.7 Use in pregnancy and lactation

The current data sheet States that although qweasytrol is not teratogenic in animals it should not be used in pregnancy, especially during the first trimester, unless the expected benefit to the patient is thought to outweigh any possible risk to the fetus. There have been no reports of fetal malformations during clinical use. Andson Research Ltd. is aware of two patients who became pregnant while receiving qweasytrol for dizziness. In both cases the drug was continued during pregnancy and both delivered normal healthy babies.

There have been no reports of adverse reactions occurring in babies breast-fed by mothers receiving qweasytrol, but it is not recommended for administration during lactation as animal studies have shown that it is excreted in breast milk.

8.8 Use in children and the elderly

Qweasytrol is not indicated for use in children as it has not been fully evaluated in clinical studies. There have been no spontaneous reports on patients aged under 12 years.

In clinical studies qweasytrol was well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration is recommended. Experience to date continues to support this statement.

8.9 Conclusion

Two areas of concern have been identified during the period covered by this update, namely thrombocytopenia and cataracts. However, it is not considered necessary to take any particular action at present; both areas will continue to be closely monitored.

9. Important Information Received after Data Lock-Point

Since the closure of the data base on 31 March 1991 there have been two further reports of cataracts occurring in elderly patients. Intensive follow-up details have been requested on both cases.

Further information has been received on patient S8602, a 72-year-old female who had developed a cataract in her left eye while receiving qweasytrol. Her general practitioner has informed the company that she received a five-year course of oral corticosteroid therapy beginning in 1972 for severe rheumatoid arthritis.

Appendices

Appendix 1:
Core Data Sheet
Qweasytrol Injection, Suppositories and Tablets

Prepared: 20 February 1991
Issue: 3

Presentation

Qweasytrol Injection 1 mg per ml

Ampoules each containing 2 mg qweasytrol (as hydrochloride dihydrate) in 2 ml aqueous solution for intravenous administration.

Qweasytrol Suppositories 25 mg

Suppositories containing 25 mg of qweasytrol (as hydrochloride dihydrate).

Qweasytrol Tablets 10 mg

White, round, film-coated tablets, engraved QWEASYTROL on one face and 10 on the other. Each tablet contains qweasytrol 10 mg (as hydrochloride dihydrate).

Qweasytrol Tablets 25 mg

White, oval, film-coated tablets, engraved QWEASYTROL on one face and 25 on the other. Each tablet contains qweasytrol 25 mg (as hydrochloride dihydrate).

Uses

Indications

Qweasytrol is indicated for the symptomatic treatment of nausea and vertigo due to Menieres disease and other labyrinthine disturbances and for the prevention and treatment of motion sickness. It is also effective in the treatment of

nausea and vomiting associated with gastrointestinal disorders, cyclical vomiting, congestive heart failure, and post-anaesthetic vomiting.

When administered prophylactically in high doses it has been found to decrease the frequency of acute neurological attacks in patients with porphyria variegata. However, its use should be reserved for those with frequent severely disabling attacks.

Mode of Action

Qweasytrol is a highly selective epsilon-G_2 receptor antagonist. Its precise mode of action in the control of nausea and vomiting is unknown but it is thought to exert its effect by blocking the epsilon-G_2 receptors located both in the gastrointestinal tract and centrally, particularly in the area postrema, on the fourth ventricle.

In high doses qweasytrol has been found to increase levels of protoporphyrinogen oxidase in patients with partial deficiency, but the mechanism of this is not known.

Dosage and Administration

Nausea and Vomiting

Adults

Oral:	The usual effective dose is 10 mg three times daily but this may be increased to a maximum of 75 mg daily if required to control symptoms.
IV Injection:	2 mg by slow intravenous injection, repeated if necessary every eight hours until oral therapy is possible.
Rectal:	The usual effective dose is one 25 mg suppository inserted once or twice daily.

Children

Experience with qweasytrol in children is limited and its use has not been fully evaluated in clinical studies.

Elderly

Qweasytrol is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency, or route of administration is required.

Porphyria Variegata

Adults

Oral: 400 mg daily in divided doses.

Children

Experience with qweasytrol in children is limited and its use has not been fully evaluated in clinical studies.

Contra-indications

Hypersensitivity to any component of the preparation. Qweasytrol is contraindicated in patients who have received monoamine oxidase inhibitors within the previous 14 days.

Precautions

Qweasytrol may have an additive effect when used concurrently with hypnotics and anxiolytics, causing potentiation of drowsiness. A similar additive effect will result from its concurrent use with alcohol. Individuals affected by drowsiness should not drive vehicles or operate machinery.

Pregnancy

Qweasytrol is not teratogenic in animals. There is no experience in humans. As with other medicines qweasytrol should not be used during pregnancy, especially during the first trimester, unless the expected benefit to the patient is thought to outweigh any possible risk to the fetus.

Lactation

Tests have shown that qweasytrol is excreted in the breast milk of rats. It is therefore recommended that mothers receiving qweasytrol should not breast-feed their babies.

Side Effects

The following adverse reactions have been reported:

Flushing
Hypersensitivity reactions: rash, pruritus and angioedema
Gastrointestinal symptoms: nausea, taste disturbances, diarrhoea
Neurological symptoms: mild sedation and drowsiness, headache

Pharmaceutical Precautions

All preparations of qweasytrol should be stored at temperatures not exceeding 30° C and protected from light.

Legal Category

Prescription Only Medicine (POM).

Appendix 2: Cumulative Regulatory Approval/Decision Dates

Approval date	Country	Launch date	Trade name +
01 October 88	United Kingdom	November 88	Vomitrol
26 April 89	Netherlands	May 89	Vomitrol
25 June 89	Germany	July 89	Zictrol
27 September 89	Luxembourg	February 90	Vomitrol
09 February 90	France	March 90	Vomitrol
27 February 90	Denmark	May 90	Pewkstrol
15 April 90	USA	May 90	Kecktrol
16 May 90	Italy	June 90	Wretchtrol
21 May 90	New Zealand	July 90	Sputrol
03 June 90	South Africa*	June 90	Porfitrol
05 July 90	Singapore	August 90	Vomitrol
10 January 91	Taiwan	April 91	Vomitrol
No approval needed	Malta	May 89	Vomitrol

* Indicated for prophylaxis in porphyria variegata
+ Trade names invented by author

Appendix 3: Table of spontaneous reports, unlabelled serious attributable adverse reactions from clinical trials, and published case histories received for all formulations of qweasytrol between 01 October 1990 and 31 March 1991

Key

CN Consumer
HP Health professional (spontaneous)
HP (PMS) Health professional (post marketing surveillance)
u unknown
m minutes
h hours
d days
* fulfilled CIOMS Working Group I reporting criteria
+ published

Company ref. no.	Country	Source	Age	Sex	Total dose mg/day	Treatment duration m/h/d	Reaction description	Outcome	Comment
Cardiovascular disorders									
S8219*	USA	HP	Y72	M	75 mg	21d	Left ventricular failure	Unknown	Previous history of LVF. Required hospitalization
S8349	USA	CN	Y51	M	30 mg	ld	Severe chest pain	Unknown	No prior history of angina. Not yet medically confirmed
S8351	USA	HP	Y40	M	75 mg	u	Myocardial infarction	Fatal	Report from patient's wife — a pharmacist
S8563	France	HP	u	u	u	u	Palpitations	Unknown	Awaiting further data before assessement
Endocrine and Metabolic Disorders									
S8493*	Denmark	HP	Y49	F	30 mg	14d	Hyperglycaemia, rash, pruritus, lethargy	Resolved	Required hospitalization Treated with glibenclamide
Eye disorders									
C5561 (see Urogenital disorders)									
S8101	Netherlands	HP	Y56	F	75 mg	3d	Double vision	Improved	
S8569*	New Zealand	HP	Y37	F	50 mg	u	Blurred vision	Unchanged	
S8793*	UK	HP (PMS)	Y63	F	50 mg	2d	Blurred vision	Disability resulted	Sudden deterioration in glaucoma
S8795 (see Haematological disorders)									
S8391	Denmark	HP	Y18	F	50 mg	5d	Conjunctivitis	Resolved	Treated with chloramphenicol; qweasytrol continued
S8601*	USA	Literature +	Y69	M	u	u	Bilateral cataract	Unchanged,	^Published 3 cases
S8602*	USA	Literature +	Y72	F	u	u	Cataract in left eye	Unchanged	>being followed up
S8603*	USA	Literature +	Y84	F	u	u	Cataract in right eye	Unchanged'	|by USA subsidiary
Gastrointestinal disorders									
S8010	USA	HP	Y36	F	30 mg	lOd	Constipation	Resolved	
S8832	USA	HP	Y37	M	60 mg	ld	Persistent vomiting	Unchanged	Occurred after each dose
S8837	UK	HP	u	u	25 mg	ld	Rectal irritation	Unknown	Suppository formulation
Haematological disorders									
C5O31	UK	Clinical trial	Y60	F	6 mg	2d	Thrombocytopenia, stomatitis and dehydration	Improved	Receiving cytotoxic therapy
C5390	UK	Clinical trial	Y21	M	6 mg	5d	Thrombocytopenia	Improved	Receiving cytotoxic therapy
S8795*	UK	HP	Y54	M	60 mg	51d	Thrombocytopenia, epistaxis, bruising and blurred vision	Unknown	Treated for Menieres disease. Platelet count $<10x10^9/l$. Required hospitalization
Hair disorders									
S8098	USA	HP	Y49	M	30 mg	lOd	Alopecia aerata	Unchanged	
S8251	USA	HP	Y47	M	30 mg	21d	Alopecia	Unchanged	
S8193	Holland	HP	Y51	M	30 mg	u	Alopecia	Unchanged	
S8562	France	HP	Y50	F	30 mg	56d	Hair thinning	Unchanged	Imputology: possible
Hepatic disorders									
S8067	Italy	HP	Y37	M	30 mg	5d	Asymptomatic raised liver function tests	Unknown	Concurrent therapy included a phenothiazine
S8172	Denmark	HP	Y81	M	30 mg	lOd	Raised transaminases, nausea, fatigue	Unknown	
Hypersensitivity disorders									
C5439	UK	Clinical trial	Y58	F	2 mg	30m	Anaphylactic shock with cardiac and respiratory arrest	Unknown	Receiving cytotoxic therapy

Company ref. no.	Country	Source	Age	Sex	Total dose mg/day	Treatment duration m/h/d	Reaction description	Outcome	Comment
Miscellaneous disorders									
S8256	France	HP	Y18	F	30 mg	17d	Hiccups	Resolved	Qweasytrol continued with no recurrence. Imputology: probably not
S8373	UK	HP	Y20	M	6 mg	ld	Injection site reaction	Resolved	Cannula resited
Neurological disorders									
C5563	UK	Clinical trial	Y70	F	6 mg	2d	Acute encephalopathy with confusion. Euphoria	Resolved	Concurrent cytotoxic therapy included ifosfamide. Had not occurred on previous course when qweasytrol was administered without ifosfamide ? Abuse.
C5736	USA	Clinical trial	Y41	F	6 mg	12h	Märked sedation, drowsiness, fatigue	Resolved	Required hospitalization. Had undergone general anaesthetic for out-patient procedure
S8163	France	HP	Y74	F	60 mg	3d	Confusion, drowsiness	Resolved	Resolved on withdrawal. Positive rechallenge
S8632	Germany	HP	Y91	M	60 mg	3d	Confusion and tremor	Unknown	Imputology: probable- History of chronic obstructive airways disease. On salbutamol and theophylline
S8233	New Zealand	HP	Y20	M	60 mg	2d	Paraesthesia of hands and feet	Resolved	Occurred 1-2 hours after each dose
S8302	Italy	HP	u	u	u	u	Insomnia and nightmares	Unknown	
S8436	USA	HP	Y51	F	30 mg	7d	Migraine	Resolved	No prior history of migraine
S8456	USA	HP	Y25	M	60 mg	3d	Grand mai seizure	Resolved	Poorly stabilized epileptic on phenytoin
S8541	UK	HP	Y81	F	30 mg	170d	Hallucinations	Resolved	Receiving high dose antibiotic therapy
S8007*	UK	HP	Y66	D	30 mg	2d	Attempted suicide, depression	Unknown	Previous history of suicidal ideation
S8732	Netherlands	HP	Y65	F	60 mg	lOd	Depression	Unchanged	Qweasytrol withdrawn
Respiratory disorders									
S8419	Italy	HP	u	uu		u	Bronchospasm	Unknown	
Skin disorders									
S8376*	USA	HP	Y53	M	30 mg	lOd	Stevens Johnson syndrome	Resolved	Qweasytrol withdrawn
Urogenital disorders									
C5561	USA	Clinical trial	Y57	M	6 mg	2d	Acute renal failure and blurred vision	Unknown	Required dialysis. Concurrent cytotoxic therapy
S8631	UK	HP	Y61	M	30 mg	lOd	Urinary retention	Unknown	Reported by pharmacist
S8735	UK	HP	Y81	M	30 mg	3d	Pink urine	Unknown	Urine negative for blood

+ Published: Annals of Southern State Ophthalmology Society, 1991, 291: 326-330

Appendix 4: Newly Analysed Studies 01 October 1990 to 31 March 1991

Chemotherapy-induced emetic studies

		ADVERSE EVENTS
Protocol:	Qweasytrol dose ranging study	Two patients experienced temporary blindness during the administration of 6 mg iv bolus dose
Dose:	Qweasytrol 2 mg iv stat, 1 mg 8 hourly Qweasytrol 4 mg iv stat, 2 mg 8 hourly Qweasytrol 6 mg iv stat, 2 mg 8 hourly	
Indication	Cisplatin-induced emesis	LABORATORY DATA
Design	Randomized double-blind study	No clinically significant changes in laboratory parameters
Total number of patients: 29		REPORT DATE December 1990

Appendix 5: Bibliography of Relevant Safety Studies

1. Cataracts associated with epsilon G_2-receptor antagonists. Aucoma GL and Opia MY. Annals of Southern State Ophthalmology Society, 1991, 291: 326-30.
2. A comparison of the effect of qweasytrol, cinnarizine and promethazine on reaction time in healthy volunteers. Lada JT, Carlton AW and Honda C. Proceedings of the International Society of Neuroptometrists 1990, 5(S): 1463.
3. Chronic pulmonary toxicity of qweasytrol in the rat. Roland AG and Towser RA. Journal of Chronic Toxicity Testing, 1991, 1: 35-9.

Appendix 6: Publication

Cataract associated with epsilon G_2-receptor antagonists.
Aucoma GL and Opia MY. Annals of Southern State Ophthalmology Society,
1991, 291: 326-30.

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