Chapter 1
Scope of the thesis
INTRODUCTION

There is a continuous need to monitor and evaluate the effectiveness and safety of medicines when they are used in daily clinical practice after their release for marketing [1, 2]. Safety is a key issue in the appraisal of drug therapy outcomes [3-5]. Drug related problems are probably one of the most frequently occurring and significant health hazards [6].

Recently, the withdrawal of five drugs from the US market in a 12-month period has raised concerns about the role of pre- and postmarketing regulations with respect to drug safety. Friedman et al have reviewed these cases and came to the conclusion that the approval dates of these removed drugs were scattered over the last decades, making a time association between the recently established reduction of review time at the FDA and the drug withdrawals not very likely [3]. Balancing the risks and benefits of drug treatment is one of the most challenging responsibilities of all stakeholders in pharma (prescribers, industry, pharmacists, regulators, academia) [4, 5].

The effectiveness, safety, and patterns of use of a drug in real life may be different than as assessed in clinical trials due to differences in prescribing physicians and patients. Key differences between clinical trials and the ‘real world’ are the limited patient numbers, restrictions in the patient populations (e.g. pregnant women, children, elderly and those predisposed to develop adverse events are frequently excluded) and the limited duration of drug use in clinical studies [4]. Effectiveness and safety when used for indications or in dosages other than initially tested remain unknown and knowledge about interactions with concomitantly used drugs due to multiple pathology is not always complete. Moreover, physicians’ prescribing habits are often unknown at the time of market entry and may vary over time due to commercial promotion, cost containment measures, changing attitudes and guidelines of therapeutic evidence [7].

Postmarketing surveillance aims to monitor and evaluate both the beneficial and adverse effects of drugs after approval for general use. The Health Council in the Netherlands has defined postmarketing surveillance (PMS) as ‘The systematic surveillance and scientific study of all intended and unintended effects of medicines on human health, after their release for marketing’ [8]. Spontaneous reporting systems have been shown to be effective in revealing unusual or rare ad-
verse events [4]. However, spontaneous reports alone do not provide sufficient evidence to conclude that an adverse event is indeed drug related. Recently, McNeil et al demonstrated the limitations of spontaneous reporting in relation to the antibiotic agent flucloxacillin [9]. There were such reports from Australia, New Zealand and UK suggesting flucloxacillin-associated jaundice, but these data were insufficient to test the hypothesis of a causal association. Spontaneous reports should be supplemented by analytical studies, monitoring of cohorts of users of new drugs, using record-linkage to track their subsequent outcomes, and to interpret the results of such analyses in the context of variability of drug exposure [7].

Several designs can be applied to investigate medicines after approval for marketing, either descriptive or analytical, and either non-experimental or experimental [2, 10-14].

Record-linkage has made a significant contribution to postmarketing surveillance of drugs, which involves linking drug exposure to outcome data (effectiveness, safety, economics) [10-12]. Even patient reporting can play an important role in pharmacovigilance, as reporting by patients may lead to earlier notice of adverse events [15].

There are many significant features of drug exposure and related outcomes to be studied in postmarketing surveillance, such as time dosing of medicines in daily use, prescription patterns, dynamics of indications and off-label use.

Examples of such topics in postmarketing evaluation of medicines include also fine-tuning of dosage recommendations, a reappraisal of indications (extension or restriction), drug use and drug users characteristics, assessment of long-term efficacy, assessment of side effects detection of unexpected side effects and interactions, long-term safety, study of potential risk groups, detection of unexpected beneficial effects, further pharmacological and mechanistic studies, and finally cost-effectiveness studies [2, 7].

Illustrations of such approaches comprise a postmarketing study regarding the teratogenetic metabolite of acitretin [16]. Furthermore, the introduction of drugs with a new pharmacological profile especially requires postmarketing surveillance of adverse events, as illustrated by the case of ibopamine [14].
Automated databases and field cohort studies in postmarketing surveillance

One of the most productive approaches in postmarketing surveillance has been the use of automated databases including ample data on drug exposure, clinical characteristics of patients and health outcomes. The European scene of the automated databases is fairly straightforward [2]. In The Netherlands, Herings et al have developed the PHARMO Record Linkage System, in the United Kingdom GPRD and MEMO are widely recognised as valuable sources for postmarketing studies, in Odense (Denmark) the so-called OPED database has been shown to be an important asset and in Italy the county of Friuli has developed a relevant database for pharmacoepidemiologic work [2, 10, 12]. In North-America (including Canada) there is ample opportunity to approach automated databases for postmarketing surveillance (e.g. large number of HMOs, Saskatchewan, Medicaid) [2]. However, automated databases frequently have important limitations regarding reliability and completeness of records on baseline health and disease status, longitudinal clinical data (e.g. course of disease, data on hypertension, cholesterol level) and health behaviour (smoking, drinking, OTC drugs) [4, 17]. In case of postmarketing surveillance of a newly launched drug, there are three other reasons why automated databases may be not the first choice for conducting postmarketing surveillance studies:

1. Selection: Adoption of a new drug by physicians is highly variable and often unpredictable due to differences in prescribing attitudes, formulary policies, and marketing practices.
2. Size: In general, the introduction of a new drug on the Dutch market hardly ever leads to a population of first users exceeding the size of 15-20,000 in the first year after marketing. Currently PHARMO for instance, covers around 2% of the Dutch population and thus can only provide information on a group of between 300 and 400 patients in the first year.
3. Access: Many databases have a lag time between data recording and availability for research (although advances in IT have led to significant improvements here).

Thus, the limitations of automated databases and the specific features of new drug prescribing have fostered the development of alternative strategies for building field cohorts of recipients of a new drug and performing follow-up monitoring and evaluation [17].
Since the early days of such field cohort studies in the late 80s, concerns have been expressed about industry bias, seeding pressure in the form of pushing prescriptions, and ethical issues related to industry sponsored postmarketing cohort studies [18-21]. Discussions began regarding whether studies performed with marketed drugs, where the physicians get paid for their participation, were scientifically justified or were simply to increase sales [22].

One of the first ‘whistleblowers’ here was Inman. He blamed industry for the promotional nature of their postmarketing surveillance studies and expressed concerns about the consequences of physicians’ participation in such studies with respect to the response rate to contribute to the prescription-event monitoring (PEM) system organised by the Drug Safety Research Unit in UK [18]. Inman found that general practitioners (GPs) heavily involved in promotional postmarketing studies were frequent prescribers of the drugs under investigation in such studies. There was a consistent inverse relation between the number of prescriptions per individual GP and the response rate to PEM. The overall response among GPs was 53%, but the heaviest 10% of prescribers returned only 44% and the heaviest 1% returned only 34% of PEM questionnaires.

Waller et al published an important analysis on industry sponsored postmarketing studies in 1992 [23]. They concluded that such studies, because of weak study design and problems with recruitment, had made only a limited contribution to the assessment of drug safety to date. Based on the recommendations of Waller et al several attempts have been made to design better and scientifically more rigorous postmarketing surveillance models. This development has led to the establishment of European guidelines for Safety Assessment of Marketed Medicines (SAMM) [24]. These guidelines were developed in draft form in 1993 by a joint committee with members with a clinical, regulatory, academic or pharmaceutical industry background in order to provide basic rules to ensure good study design. A legal framework is given in Council Regulation (EEC) No 2309/93 (Title 2, Chapter III) and Council Directive 75/319/EEC as amended (Chapter Va) [25]. The obligations apply to all authorised medicinal products, are clarified in the draft-Notice to Marketing Authorisation Holders and incorporate among other things that the design of company sponsored postmarketing surveillance studies will depend on the objectives of the study, which must be clearly defined in the study protocol. Specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. Although the
SAMM guidelines cover different designs of studies (observational cohort studies, case-control studies, case-surveillance and clinical trials) they have mainly been used for the conduct of cohort studies [26, 27].

At present, several European countries have published guidelines for the conduct of postmarketing studies in accordance with the above-mentioned guidance of the European Union. Promotional activities conducted under the guise of postmarketing studies remain unacceptable. The field of such studies shows a continuous process of ‘trial and error’ of finding the right balance between scientific work, involvement of health practitioners and patients and promotional activities. Although the SAMM guidelines provide a useful format for finding the right balance, postmarketing practice has shown several cases of studies leading to debate and critique. Ayres et al have reported from a postmarketing surveillance study to evaluate the safety of a non-chlorofluorocarbon metered dose salbutamol inhaler [28]. This study was conducted according to the SAMM-guidelines and was a comparison of safety in patients using prescribed metered doses of salbutamol delivered by inhalers using either hydrofluoroalkane or chlorofluorocarbon as the propellant. There were no significant differences in hospitalisations and reports of adverse effects between the hydrofluoroalkane and chlorofluorocarbon inhaler groups. Although the study design successfully fulfilled the recommendations of the SAMM guidelines, several authors have criticised the study for being promotional, and for being unethical [29, 30].

On the other hand one sees an increasing visibility of industry in types of postmarketing surveillance studies resulting in clinically relevant findings [31, 32]. Although general maturity is not yet established, there is an increasing awareness among industry pharmacovigilance and pharmacoepidemiology professionals to continue in challenging their marketing colleagues to improve standards within the industry. Moreover, academic pharmacoepidemiology has increased its contribution significantly to drug safety studies and is now representing a strong partner in solving important drug risk questions [33, 34].

**PERSPECTIVE OF THE STUDY**

With this background of interest in postmarketing research and the recognised additional value of results of postmarketing surveillance studies, Aventis Pharma B.V. and Janssen-Cilag B.V. took the initiative to set up the Peptic Survey proj-
Peptic Survey was a postmarketing surveillance study with lansoprazole, the second proton pump inhibitor (PPI) introduced on the Dutch market at the end of 1993 by the previously mentioned pharmaceutical companies [35]. At the time of product launch, the drug was indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers. The drug was introduced at first as a 30 mg capsule, while in January 1996 a 15 mg capsule was launched for the same indications. At the time of introduction, lansoprazole had been evaluated in several thousands of patients enrolled in clinical trials. The widespread use of PPIs justified a thorough assessment of the safety of these drugs. The study started soon after the introduction of lansoprazole on the Dutch market. All objectives were clearly defined in the study protocol and/or amendments of the protocol.

**Objectives**

The primary objectives of this study were to assess the safety and effectiveness of lansoprazole in a population composed of naturally occurring groups of users and to evaluate the patterns of use of lansoprazole in daily practice. Secondary objectives were to identify factors related to non-reponse to lansoprazole, headache or diarrhoea during lansoprazole use and to evaluate the use of lansoprazole as part of a *Helicobacter pylori* (*H. pylori*) eradication therapy.

**Design**

The study was a prospective, open label, observational follow-up study carried out in naturally occurring users of lansoprazole in the Netherlands. The total duration was aimed to be at least two years, and in fact was extended to 4 years and 3 months. The study protocol was designed in the fall of 1993, whereas European guidelines for the design of company sponsored postmarketing surveillance studies at first became available in December 1993.

Nevertheless, the design incorporated five of the six recommendations of the European SAMM guidelines, namely:

1. A population as representative as possible of the general population of users, and not selected. No in- or exclusion criteria were considered;
2. The medicinal product must be prescribed in the usual manner;
3. Patients must not be prescribed the medicine in order to include them;
4. The decision to prescribe must be clearly separated from the decision to include the patient in the study;
5. The protocol stipulated the maximum number of patients to be entered by a single physician [24].

The recommendation to include an appropriate comparator group was not followed. This was due to two reasons; firstly, at the time of initiation of our study only one other PPI was available on the Dutch market, which limited our choice. Secondly, for reasons of efficiency we chose to make use of internal comparisons in the analyses. As advised in the guidelines an independent scientific advisory group was appointed to monitor the data and to oversee the study.

For day-to-day management a project team was installed. This team consisted of an independent chairman, a project leader of Aventis Pharma B.V., a member of Janssen-Cilag B.V. (during the first phase) and a member of the independent Contract Research Organisation Kendle. The Medical Ethical Committee of the Utrecht University Medical Centre approved the protocol. The highest standards of professional conduct and confidentiality were maintained throughout the study. All data and documents were kept in strict confidence and in accordance with the privacy regulations.

Study population

All GPs, internists and gastro-enterologists in The Netherlands were invited to participate in the study (Appendix I). In order to avoid inclusion bias, participating physicians and pharmacists were remunerated with only a modest fee, equivalent to the reimbursement of their time spent to complete the record forms or generate the medication histories. GPs could include a maximum of 20 patients per two years follow-up time, while specialists were allowed to include not more than 50 patients in the same period. It was estimated that 5,000 to 10,000 patients, to whom lansoprazole was prescribed in daily practice, might participate in this study following the recommendations available at that time. All procedures of patient inclusion, data recording and monitoring were designed not to influence normal prescribing practice. Lansoprazole was prescribed without any form of intervention or randomization. The patients’ pharmacist, as part of routine pharmaceutical care, provided the medicines.
All patients having used, or using lansoprazole, could be included in the study at the first visit or any later follow-up visit after lansoprazole was prescribed. The decision to prescribe was therefore clearly separated from the decision to include the patient in the study. Furthermore, patients could not be prescribed the medicine in order to include them, but must be natural occurring lansoprazole users. Patients were informed about the project and agreed to participate by giving their written informed consent to allow access to all relevant clinical and medication data and storage and analyses of these data (Appendix II). No further selection criteria were considered. All lansoprazole users could be included independent of for example, age, indication for use, co-morbidity, and use of co-medication. To maintain patient anonymity patients were identified by an identification code only. All data and documents related to patients included were kept in strict confidence and in accordance with Dutch privacy regulations.

Data were collected at the inclusion visit and at follow-up visits during lansoprazole therapy by reviewing the medical file and by patient questionnaire. Data collection was designed not to influence daily practice. No supplementary diagnostic tests were requested from the physician with regard to the indication. Complete medication histories were constituted through pharmacy records six months retrospectively and during the lansoprazole therapy. Computerization of pharmacy records, and thus the compilation of medication histories, is almost universal in the Netherlands. The majority of patients are designated to a single pharmacy for all reimbursed prescription drugs. In our study, the physician requested the appropriate pharmacy to collect the pharmacy records.

For a subset of patients included after December 31st 1995 additional evaluation forms regarding headache, diarrhoea and/or lack of effectiveness were completed by the physician and, where applicable, after consultation with the patient in question. In addition, for all patients during the total study period where lansoprazole was used as part of a *H. pylori* eradication therapy, additional evaluation forms were completed by the physician.

To ensure the collection of accurate, consistent, complete and reliable data participating physicians were instructed and monitored in completing the forms at regular intervals by representatives of the pharmaceutical companies and/or the independent Contract Research Organisation.
All data collected by the participating physicians and pharmacists were entered in databases, validated and analysed by the independent Contract Research Organisation in conjunction with the Department of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (UIPS). Inquiries were made in case of inconsistencies, incorrect data, and missing data. The decision to communicate or to publish depended upon the scientific merit and interest in the findings and was agreed by the independent scientific advisory group. The authors of all publications were not associated with the sponsors of the study.

During the first two years data of 5,669 patients were analysed, resulting in two chapters of the thesis (Chapters 2.1 and 4.2). The second two years another 4,339 patients were included. The total number of 10,008 patients comprised the source of all other chapters.

OUTLINE OF THE THESIS

In Chapter 2 of the thesis the general response to PPI therapy of the project Peptic Survey is given. The design of the study is described in detail and the results of the primary objectives regarding safety, effectiveness and patterns of use are captured in Chapter 2.1. Since PPIs have a high efficacy, we were interested to identify possible co-factors associated with lack of effectiveness during lansoprazole use (such as compliance, diagnosis and acid-relatedness of complaints). For this reason we compared patients with lack of effectiveness on treatment (‘non-responders’) versus control patients without lack of effectiveness on treatment (‘responders’) in Chapter 2.2.

In Chapter 3 drivers of PPI treatment were the key elements of our investigation. In Chapter 3.1 we investigated the increasing amount of combined prescriptions of NSAIDs and PPIs. We assessed how frequently PPIs were prescribed in combination with NSAIDs in order to prevent acid related disorders and to treat NSAID induced acid related disorders. In Chapter 3.2 we investigated whether the study has led to selection bias regarding inclusion of patients in the study and whether the design of this study was susceptible to driving prescriptions.

The role of *H. pylori* and the role of PPIs in the eradication of *H. pylori* have become very important in the last years. In addition to existing results of clinical
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Trials, a study was set up to investigate the characteristics and the effect of time of *H. pylori* eradication therapy in daily clinical practice of lansoprazole users. This research is captured in Chapter 4.1.

Therapies combining antibiotics and PPIs, including dual, triple and quadruple schedules have been shown to be effective in clinical trials to eradicate *H. pylori* in peptic ulcer patients, whether this results in improved symptoms in clinical practice remains unclear. In Chapter 4.2, we investigated continued use of lansoprazole treatment after *H. pylori* eradication therapy and evaluated possibly related determinants of such continuation in daily clinical practice.

In Chapter 5, the safety of lansoprazole in 10,008 users was assessed. Frequencies and incidence densities were calculated for all adverse events and the pattern in time was given, as can be read in Chapter 5.1. In addition, two subsets were used to investigate two frequently reported adverse events during lansoprazole use, namely headache and diarrhoea. Besides the high prevalence, these adverse events often lead to a discontinuation of a PPI. These subsets were used to investigate the frequency and characteristics of the adverse event during lansoprazole use and to possibly find relevant co-factors associated with the occurrence of the adverse event by comparing patients with the occurrence of the adverse event to those without. These results are given in Chapter 5.2 and 5.3.

Chapter 6 gives a summary of the findings and a discussion of the implications of our results.
REFERENCES


29. Bamber MG. Postmarketing surveillance study of a non-chlorofluorocarbon inhaler. Such studies initiated by manufacturer are designed to promote product. BMJ 1999;318:810.