CLINICAL INVESTIGATION OF ORAL CONTRACEPTIVES

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Additional Notes: This note for guidance is intended to assist applicants for a marketing authorisation in the interpretation of Directive 75/318/EEC as amended with respect to specific clinical problems involved in establishing the safety and efficacy of oral contraceptives. A contraceptive preparation consisting of two or more components should also be investigated so as to elucidate the points listed in the note for guidance on Fixed-Combination Medicinal Products.

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1. GENERAL

This note for guidance should be read in the light of the annex to Directive 75/318/EEC as amended as well as Directive 65/65/EEC as amended; it is intended solely to assist applicants in the interpretation of these documents with respect to the specific clinical problems involved in establishing the safety and efficacy of oral contraceptives.

This note has been compiled primarily with those contraceptives in mind which have hormonal activity and are administered orally to women. It is evident that for other contraceptive products subject to medicines legislation the investigational approach required to assess efficacy and safety will be analogous but not necessarily identical.

A contraceptive preparation consisting of two or more components should also be investigated so as to elucidate the points listed in the note for guidance on Fixed Combination Medicinal Products, i.e. the properties of the individual components and their contribution to the total effect should be known.

Where a new contraceptive can be considered as a modification of one already recognised as being efficacious and safe (particularly where there is merely a minor change in dosage, or where one oestrogen is replaced by another accepted oestrogen) it may be possible to simplify the investigations provided the theoretical basis for the new formulation appears to be sound.

2. CLINICAL-PHARMACOLOGICAL STUDIES

Clinical-pharmacological studies performed with an oral contraceptive (and in the case of a fixed combination also with its components) are most likely to meet the standards set by the annex to Directive 75/318/EEC as amended if they are designed to provide data on:

a) the pharmacological action or actions in man by virtue of which a contraceptive effect is attained;

b) other pharmacological effects on the reproductive system and process, including those on hypothalamic and pituitary activity, ovarian endocrine secretion, ovulation, endometrial histology and biochemical activity, cervical mucus and vaginal cytology and secretion. Effects on tubal function, which cannot currently be studied in human subjects, can be investigated in animals;

c) the degree of progestogenic, oestrogenic, androgenic, corticosteroid and other hormonal or anti-hormonal activity of the product and its components in man. It is appreciated that the quantitative study of some of these effects (particularly androgenicity and anti-androgenicity) in the clinical pharmacological phase may be difficult, but conclusions on these points may also be drawn from animal studies and from adverse reactions occurring during efficacy investigations;

d) the nature and hormonal activity of the principal metabolites;

e) suspected medicinal product interactions likely to impair the efficacy of the product;
f) those adverse effects likely to be detectable with products of this type even in a limited population, including those involving liver function, adrenal activity, lipid and carbohydrate metabolism, the thyroid and haemostatic mechanisms.

3. CLINICAL INVESTIGATIONS OF EFFICACY AND SAFETY

Clinical studies with an oral contraceptive are most likely to meet the standards set by the annex to Directive 75/318/EEC as amended if the following principles are borne in mind:

a) Trial population

The population studied should be reasonably comparable to that in the country or countries in which it is proposed to introduce the product. It should be realised that dietary habits, endemic diseases, body weight, illiteracy, etc. can substantially affect the results obtained with a given contraceptive method.

b) Scope of trials

The clinical investigation should be sufficiently large to render possible a reliable calculation of efficacy (in terms of the Pearl Index and the Life Table method) and of the incidence of adverse reactions. In practice it generally proves desirable for an entirely new contraceptive product (e.g. one incorporating a new progestagen) to study some 20,000 cycles of treatment. Where a modification of an existing product is investigated, valid conclusions may sometimes be drawn from more limited material.

Since both the effect of the product and the degree of precision with which it is used may alter during long-term use, a substantial part of the total population studied should have used the contraceptive for a period of not less than 12 months, e.g. about a quarter of the total data available should relate to prolonged use.

Although any large-scale study of an oral contraceptive will as a rule have to be conducted on a multicentre basis, only data from those centres which have gained substantial experience with the product should be included in the total analysis.

c) Studies on admission

History-taking and clinical examination at the time of admission to the trial should provide a detailed record of any risk factors, relative contra-indications or other elements which may subsequently be relevant to the assessment of efficacy and supposed adverse effects, e.g.:
- age,
- obesity,
- smoking habits,
- alcoholism,
- cardiovascular disease,
- psychic disorders or symptoms,
- migraine,
- endocrine and metabolic disorders,
- epilepsy,
- anaemia,
- disorders of the haemostatic system,
- renal disorders,
- hepatic disorders,
- tumours.

The prior obstetric, gynaecological and contraceptive history should be known and recent and current medicinal product intake recorded. The findings on certain of the above points will clearly lead to the exclusion of some subjects from the trial.

d) Recording of data

It is recommended that in a contraceptive study individual patient data be recorded on a well-recognised form, such as that advocated by the World Health Organisation. Trial subjects should be seen by investigators at intervals of not more than three months.

In all subjects taking part in such studies there should be a periodic gynaecological examination including cervical smear, as well as examination of the breast, weight and blood pressure, a test of glycosuria, and a close record of the menstrual history and any suspected adverse reactions. Intercurrent illness as well as adverse events noted by the patient should be recorded and any change in libido registered.

In a subgroup detailed laboratory examinations should be performed to detect any change in the normal endometrium, hepatic function, lipid metabolism, haematological parameters, protein spectrum, serum electrolytes urine composition, adrenal activity, carbohydrate metabolism, and any parameter an effect on which might be anticipated in view of the pharmacological and toxicological findings. Where clear abnormalities are detected, the patient should be examined clinically and the findings recorded, irrespective of whether the subject continues to take part in the trial or not.

Any patients admitted to the study despite the presence of certain risk factors or functional disorders at the time of admission, should undergo regular re-examination in these respects during the trial.

In cases of contraceptive failure, data on the pregnancy and the condition of the neonate or embryo should be recorded and the possibility of patient failure assessed.

Where a subject withdraws from the study the reasons for withdrawal should be recorded and where possible the subject should be followed up to determine the time of resumption of menstruation and fertility and any possible effect on subsequent pregnancy.

Follow-up. Any subject who has shown significant variation in metabolic functions should be followed up to determine if and when these return to normal after termination of the trial.

e) Analysis of data

i) General

Data relating to efficacy, cycle control, adverse reactions and laboratory findings should be presented for the investigational programme as a whole and for the individual studies and also analysed to try and find correlations with factors likely to be capable of affecting the findings.

ii) Efficacy

If pregnancies have occurred during the study, a detailed analysis of each individual case should be presented.
iii) Cycle control

Data on cycle control should be recorded and presented in such a manner that the incidence and severity of menstrual irregularity, spotting, breakthrough bleeding and amenorrhoea are clear, and so that any variation therein between individuals or over a period of time can be discerned. It is useful to indicate to what extent such events have been regarded as acceptable by the trial subjects and the investigators.

iv) Laboratory findings

Abnormal laboratory findings should be analysed, inter alia, with respect to any possible correlations with clinical findings in the subjects concerned.

f) Absolute and relative efficacy and safety

An oral contraceptive is likely to be regarded as effective if the degree of contraceptive efficacy attained when the product is employed under field conditions by a normal population is not less than that currently attained with other contraceptive methods which have obtained wide acceptance. Some lesser degree of efficacy may be acceptable if it is outweighed by advantages in terms of safety and tolerance, and provided the chances of contraceptive failure can be quantified and are clearly explained in the texts made available to the user.

An oral contraceptive is likely to be regarded as not harmful if its adverse effects are not more severe or prolonged than those of oral contraceptives in current use, and provided that it does not result in persistent derangement of the menstrual bleeding pattern during long-term use or persistent changes after withdrawal.

g) Post-marketing studies

Whilst Directives 65/65/EEC as amended and 75/318/EEC as amended impose no requirements that post-marketing studies be conducted, applicants proposing to market oral contraceptives of a new type are urged to consider the possibility of continuing long-term clinical investigations and monitoring subsequent to introduction of the products concerned; this will greatly facilitate the assessment of reports on supposed adverse reactions.