CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-090

MEDICAL REVIEW(S)

MAR 7 2000

Division Director Memorandum
New Drug Application

NDA#:	21,090
Sponsor:	Organon, Inc.
Drug:	Cyclessa™
Generic Drug Name:	——— (Desogestrel and Ethinyl Estradiol tablets)
Indication:	Contraception
Dose:	100 µg desogestrel/25 µg ethinyl estradiol (menstrual cycle days 1-7) 125 µg desogestrel/25 µg ethinyl estradiol (menstrual cycle days 8-14) 150 µg desogestrel/25 µg ethinyl estradiol (menstrual cycle days 15-21) Inert tablets (menstrual cycle days 22-28)
Formulation:	Oral tablet
Date of submission:	May 7, 1999
Date of memorandum:	March 7, 2000

Background

CTR 77 (Trade name, Cyclessa™) is a triphasic combined oral contraceptive containing ethinyl estradiol (a synthetic estrogen commonly found in oral contraceptive products) and desogestrel [DSG] (a third generation synthetic progestin). Third generation synthetic progestins were developed to minimize the androgenic effects associated with first or second generation progestins without loss of desired progestational effects.

Three other DSG-containing oral contraceptives have been approved by the FDA, two of which are marketed by the sponsor of the current application. These two products are: (1) Desogen (a monophasic preparation containing 150 µg of DSG combined with 30 µg of ethinyl estradiol on menstrual cycle days 1-21) and Mircette (a biphasic preparation containing 150 µg of DSG combined with 20 µg of ethinyl estradiol administered during menstrual cycle days 1-21, followed by 10 µg of ethinyl estradiol alone administered on menstrual cycle days 24-28).

CTR 77 is a triphasic oral contraceptive that contains a lower total dose of DSG per cycle compared to Desogen and Mircette and a total dose of ethinyl estradiol per cycle that is lower than that found in Desogen but higher than that found in Mircette. Per the sponsor, these total cycle estrogen and progestin dose modifications were developed to maintain contraceptive efficacy and cycle control while possibly lowering cardiovascular risk.

Efficacy for CTR 77 was demonstrated in two multi-center, randomized, open-label, active-controlled trials of six months duration (i.e., Study 092001 and Study 092002). The trial arms for both studies were: (1) CTR 77; (2) CTR 99 ([redacted] that is [redacted]); (3) Ortho-Novum 777. Because the studies were of identical design, data analyses for these studies were pooled.

Study 092001 enrolled a total of 4237 women, 1392 of whom received CTR 77, accounting for 7324 cycles of exposure to CTR 77. Study 092002 enrolled a total of 4238 women, 1376 of whom received CTR 77, accounting for 7203 cycles of exposure to CTR 77. A total of 2768 participants enrolled in the two phase 3 studies received CTR 77, accounting for a total of 14,527 cycles of exposure to this drug product. A total of 2260 participants completed six cycles of drug exposure.

Because of inconsistencies noted during a DSI inspection of one clinical investigation site (site # 12 in Study 092002, principal investigator, Nancy Fordyce, MD), data from this site was excluded from efficacy analyses. In addition, another principal investigator (Dr. Robert Fiddes, site #64 in Study 092002) was convicted of falsifying data in this and other investigational drug studies. Data from his site were excluded from efficacy analyses by the sponsor prior to NDA submission, but safety data were included and reviewed.

Contraceptive effectiveness was based upon the occurrence of pregnancy in the intent-to-treat evaluation group for CTR 77. A combined Pearl Index for the 2 studies (excluding data from sites # 12 and 64 of Study 092002) of 1.0 was noted for all patients in the CTR 77 arm. Since inclusion criteria permitted enrollment of women between the ages of 18-50 years, the total number of women between the ages of 18 and 34 who received CTR 77 was 2235, accounting for 11,609 total cycles of drug exposure. The Pearl Index for women aged 18-34 who received CTR 77 was 1.14 per 100 woman-years of use. Both Pearl Indices support the contraceptive effectiveness of this product.

Safety analyses for the product revealed comparable menstrual bleeding patterns between CTR 77 and Ortho Novum 777 and an acceptable menstrual bleeding profile for CTR 77. In addition, the pattern of adverse events seen with CTR 77 was comparable to that seen with other third generation oral contraceptives.

Of note, a single venous thromboembolic event (VTE), namely a deep venous thrombosis (DVT) occurred in a CTR 77 user. This event was diagnosed on day 21 of cycle #1 of CTR 77 exposure. As described in the secondary statistics review, the point estimates of VTEs (including

DVTs and pulmonary emboli [PEs]) per 1,000 subjects and per 100,000 women-years of use with their associated 95% confidence intervals were calculated for CTR 77 and for other approved third generation oral contraceptive products. These point estimates for CTR 77 were not unusual when compared to other approved desogestrel-containing oral contraceptives.

As noted in the product labeling for all FDA-approved DSG-containing oral contraceptives, third generation oral contraceptive products have been reported to have a relative risk for venous thromboembolism of 1.5 to 2.4 when compared to certain second generation oral contraceptives. This increase in relative risk for these products was determined primarily from three large scale, epidemiologic studies, two of which were case-control studies and one of which was a cohort study [1,2,3]. This risk would translate into an additional 1 to 2 cases of venous thromboembolism per 10,000 women-years of use. The safety concern regarding the increased relative risk for VTEs with DSG-containing oral contraceptives was therefore incorporated into the labeling for CTR 77.

Modifications in the WARNINGS and PRECAUTIONS sections of the label were proposed by FDA. These modifications included changes in text related to (1) the [redacted] (2) the possibility of drug-drug interactions with desogestrel; (3) the increased risk for VTE with third generation oral contraceptive products as compared to second generation oral contraceptive products.

A final review issue related to the *in vitro* dissolution specifications for CTR 77 and resulted in a phase 4 commitment by the sponsor to perform dissolution testing at 15 and 30 minutes on the first three commercial batches of each strength of CTR 77 produced at 40°C/75%RH up to 6 months and 25°C/60%RH up to 12 months. This data will be submitted to the division when 12 months of dissolution data are available.

On 3/6/00, the sponsor contacted the division and stated that they were not prepared to accept the FDA's proposed modifications in the labeling for CTR 77 and would not be submitting a revised version of the label for negotiation prior to the action date for the application (i.e., 3/7/00). This position was reconfirmed with them during another teleconference held on 3/7/00. During the latter teleconference, the division informed the sponsor that an approvable action would therefore be taken on their application by 3/7/00.

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1 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effects of Different progestagens in low estrogen OCs on venous thrombolic disease. *Lancet* 1995; 346: p. 1582-1588.

2 Spitzer WO et al, Third generation oral contraceptives and risk of thromboembolic disorders: an international case-control study. *British Medical Journal* 1996; 312: p. 83-88.

3 Jick H et al., Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; 346: p. 1589-1593.

Recommendations:

I agree with the conclusions of the primary and secondary reviewers that the effectiveness of CTR 77 was demonstrated in the phase 3 trials and that the study data contained in the NDA support the safety of CTR 77 as an oral contraceptive. This application will be approvable pending resolution of the labeling issues and text modifications noted above.

/S/ 3/7/00

Susan S. Allen, MD, MPH
Acting Director, HFD-580

Cc: NDA 21-090
HFD-580/Allen/Davis
HFD-103/Houn/Raczkowski

APPEARS THIS WAY
ON ORIGINAL

GROUP LEADER MEMORANDUM
NDA 21-090

DEC 20 2000

Drug	**Cyclessa™**
Generic Drug Name	**(desogestrel/ethinyl estradiol tablets)**
Dose	**100 µg desogestrel + 25 µg ethinyl estradiol on days 1-7** **125 µg desogestrel + 25 µg ethinyl estradiol on days 8-14** **150 µg desogestrel + 25 µg ethinyl estradiol on days 15-21** **placebo days 22-28**
Indication	**prevention of pregnancy**
Applicant	**Organon, Inc.**
Date of Submission	**October 20, 2000**
Date of Memorandum	**December 20, 2000**
Reviewer	**Dena R. Hixon, M.D., FACOG** **Team Leader, DRUDP**

Summary

The current submission, a complete response to an Approvable letter dated March 7, 2000, is adequate to support marketing approval for Cyclessa™ in the U.S. with minor labeling revisions as communicated to the sponsor on December 18 and December 20, 2000.

Background

Cyclessa™, also known as CTR 77, is a triphasic oral contraceptive containing desogestrel and ethinyl estradiol (EE). Desogestrel is a third generation progestin developed with the goal of achieving the desired progestational effects while minimizing androgenic effects. The sponsor proposes that Cyclessa™ will maintain contraceptive efficacy with a regular menstrual bleeding pattern despite a lower dose of EE and a lower total progestin dose than in the sponsor's already approved desogestrel-containing oral contraceptive (OC) Desogen.

The only unresolved issue at the time of the Approvable action was product labeling. FDA required text in the label to address the potential increased risk of venous thromboembolism with OCs containing desogestrel, a third-generation progestin, compared to OCs containing certain second generation progestins. The sponsor disagreed

with the agency's position and presented literature references in support of omitting such text from the labeling for their other desogestrel-containing OC, Mircette™.

After an extensive review of the pertinent literature, the agency concluded that the preponderance of evidence supports the requested labeling: "Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate two-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this two-fold increase in risk." The sponsor is required to include this text in labeling for all of its desogestrel-containing products.

Efficacy of Cyclessa™

In the original NDA submission, 2 large Phase III trials of 6 months duration supported safety and efficacy of this product for marketing in the U.S. A total of 2768 women were treated with Cyclessa™ for a total of 14,527 cycles. Twelve pregnancies occurred during treatment, giving a Pearl Index (PI) of 1.08 pregnancies per 100 women-years of Cyclessa™ use. These resulted in 5 live births, 2 spontaneous abortions, 4 induced abortions, and one unknown outcome. Only 3 of the 12 pregnancies occurred with "perfect use" of the product. Three pregnancies were identified during follow-up and dates of conception ranged from 15 to 35 days after last intake of Cyclessa™.

Reviewer's comment

- *64% of Cyclessa™ users switched from another OC at enrollment, and only 6% were first-time-ever OC users.*
- *Women up to 50 years of age were included in these trials (85% between age 20 and 39). For women age 18-34, there were 11 pregnancies in 893 woman-years of Cyclessa™ exposure, giving a Pearl Index of 1.23 per 100 woman-years. In women age 35-50, there was 1 pregnancy, giving a PI of 0.45.*
- *Routine pregnancy testing was done only at baseline and at the End of Study visit. Additional testing was done as needed for suspicion of pregnancy.*

Bleeding Patterns

Bleeding patterns were evaluated from information recorded on daily diary cards by the subjects in the Phase III trials. The mean duration of withdrawal bleeding was 5 days for Cyclessa™ users. Absence of withdrawal bleeding was recorded in 3% of cycles, early withdrawal bleeding in 6% of cycles, and intermenstrual bleeding in 11% of cycles (including breakthrough bleeding in 3.5%, and breakthrough spotting in 8%).

Thirty-four Cyclessa™ users discontinued the trials due to menstrual problems, including abnormal uterine bleeding, premenstrual tension, and dysmenorrhea.

Reviewer's comment

[redacted]

Safety and Tolerance of Cyclessa™

In the Phase III studies, 1.4% of Cyclessa™ users experienced SAEs. Only 3 of these were possibly related to the study drug, one case each of cholecystitis, vascular disorder (carotid artery aneurysm), and deep thrombophlebitis (DVT). Two subjects died, one from asphyxiation and one from a scuba-diving accident. There were no myocardial infarctions or strokes.

The one DVT occurred in a 38-year-old non-smoker with a 5 year past history of OC use. After 20 pills in the first cycle, she was admitted with extensive thrombosis of the left deep venous system.

The overall adverse event profile for Cyclessa™ was similar to that seen with other COC trials. Eighteen percent of subjects discontinued the trials before completing 6 cycles of use, and 4.4% of Cyclessa™ subjects discontinued because of a drug-related adverse event.

Laboratory data from the Phase III trials showed no apparent adverse effect on fasting serum glucose, total cholesterol, or triglycerides in up to 6 cycles of exposure. There were statistically but not clinically significant differences between Cyclessa™ and Ortho-Novum 7/7/7 in mean cholesterol and triglyceride changes.

The safety update in the current submission provides no new safety information, as the clinical trials are completed and the product has not yet been marketed anywhere in the world.

Reviewer's comment

The safety and acceptability profile is similar to that seen in other trials of combined OCs. The occurrence of a single DVT supports the need to include the required labeling text regarding possible increased risk of VTE with third generation progestins.

Labeling

The Medical Officer recommended in the original review that specific information be included in the label regarding the number of women in clinical trials and the Pearl Index for pregnancies. Subsequent discussions between the Division and the Office of Drug Evaluation III resulted in a decision not to use detailed efficacy information in contraceptive labels because of differences in various contraceptive study designs.

In the current submission, the sponsor has included the text that the Division recommends for all third generation progestins regarding a possible increased risk for VTE.

In the chemist's review of carton labeling in the previous review cycle, additional information was needed for the immediate container. The sponsor confirmed in a letter dated December 19, 2000 that the company name, expiration date, and lot number will be included on the final printed labeling for the blister pack lidding foil for the trade, clinic and professional sample presentations, as previously stated on January 24, 2000.

Phase IV commitment

In the previous review cycle, on 3/2/2000, the sponsor agreed to implement the dissolution specification Q [redacted] after 15 minutes for the release specification and the specification of Q [redacted] after 30 minutes for the stability specification, with Phase IV commitment to perform dissolution testing at 15 and 30 minutes on the first 3 commercial batches of each strength of Cyclessa ™ (desogestrel/ ethinyl estradiol) product at 40^0C/75%RH up to 6 months (at 3, 6 months) and 25^0/50%RH up to 12 months (at 3, 6, 9, and 12 months). Data are to be submitted to the Division when 12-month dissolution data are available, at which time an evaluation of the specification will be made.

Clinical Assessment and Recommendations

I agree with the primary reviewer that the labeling submitted from the sponsor is acceptable for approval of Cyclessa™ for marketing with the revisions sent to the sponsor on 12/18/00 and 12/20/00.

The sponsor is requested to implement dissolution specifications as per the 3/7/00 Approvable letter, with the Phase 4 commitment to perform dissolution testing and on commercial batches of each strength of Cyclessa™.

/S/ 12/20/00

Dena R. Hixon, M.D., FACOG
Team Leader/DRUDP

/S/ 12/20/00

Susan S. Allen, M.D., MPH
Director/DRUDP

Cc: HFD-580/S. Allen/D. Shames/D. Hixon/D. Davis

MAR 7 2000

Group Leader Memorandum

NDA:	**21-090**
Drug:	**Cyclessa™ (CTR 77)**
Dosage Form/Route:	**Tablet/Oral**
Strength:	**100 mcg desogestrel/25 mcg ethinyl estradiol-Days 1-7** **125 mcg desogestrel/25 mcg ethinyl estradiol-Days 8-14** **150 mcg desogestrel/25 mcg ethinyl estradiol- Days 15-21** **Placebo-Days 22-28**
Applicant:	**Organon, Inc.**
Original Submission Date:	**May 10, 1999**
Assigned for Review:	**January 13, 2000**
Date of Memorandum:	**March 6, 2000**

Background

In this application, the Sponsor is seeking approval for a 28-day 7/7/7-type regimen of a triphasic oral contraceptive combination of desogestrel and ethinyl estradiol. There is currently no triphasic oral contraceptive (OC) containing the progestin desogestrel approved for use in this country. The formulation of Cyclessa (CTR 77) provides for a lower overall cycle dose of both desogestrel and ethinyl estradiol than does the monophasic desogestrel and ethinyl estradiol combination available in Desogen (this Sponsor) and Ortho Cept (R.W. Johnson). In support of this request the Sponsor has submitted the results of two multicenter, randomized, open-label, active comparator, efficacy and safety trials and three relative bioavailability studies.

[redacted]

[redacted] and a new clinical program for a triphasic desogestrel/ethinyl estradiol formulation was begun. On June 21, 1994, IND 45,548 was submitted for review. It contained the protocols for two identical three-arm trials with CTR 77, CTR 99 [redacted] and Ortho-Novum®7/7/7 for six months and 10,000 cycles of use. These new

protocols were reviewed and allowed to proceed. The reviewer noted that with the [redacted] the Sponsor was introducing two different triphasic formulations with intent to provide improved safety and comparable efficacy to CTR-04 (Desogen®). Pre-NDA clinical and CMC meetings were held between the Division of Metabolic and Endocrine Drug Products (DMEDP) and the Sponsor on 5/16/95 and 10/17/95, respectively. Significant agreements from those meetings included the following: a follow-up meeting would be held between the statistical reviewer and the Sponsor to discuss sample size; the NDA would include between-study comparisons of the steady state pharmacokinetics for [redacted] CTR 77 [redacted] On 2/5/96, it was agreed that a cross-reference to both the CTR-04 (Desogen) and [redacted] INDs and NDAs would provide the pre-clinical section of the new NDAs (CTR 77 [redacted] On 5/18/98 a pre-clinical NDA teleconference was held between the Division of Reproductive and Urologic Drug products (DRUDP) and the Sponsor, in which DRUDP agreed to honor previous agreements between the Sponsor and DMEDP. NDA 21-090 for CTR 77 was received on May 7, 1999.

Following completions of the clinical studies, studies 092001 and 092002, one of the principle investigators, Dr. Robert Fiddes (site 64 092002) was charged and subsequently convicted of falsifying data in drug studies for several pharmaceutical companies. Dr. Fiddes data was excluded from the Sponsor's and reviewer's efficacy analysis. The Fiddes site was included in the All-Subjects- Treated Analysis of the Safety data.

Chemistry/ Manufacturing

The Chemistry reviewer noted the following deficiencies that were addressed with the Sponsor. If available, the Division requests additional acceptance testing performed on the incoming batches of drug substances. A request to tighten stability specifications for related substances to [redacted] for individual impurity and [redacted] for total impurities. The stability commitment should be revised to include the statement "the extension of the expiration date will be based on the real time data from the first three commercial production batches". Based on the available real time stability data, a tentative expiration date of [redacted] at 25 C 60 %RH is recommended. The immediate container should have the name of the firm, expiration date and lot #. The Sponsor adequately addressed these comments. It was agreed that the Sponsor would implement the following dissolution specifications, Q [redacted] after 15 minutes for release and Q [redacted] after 30 minutes for stability.

From a Chemistry, Manufacturing and Control point of view it was determined that the NDA could be approved. A Phase 4 commitment was sought from the Sponsor to perform dissolution testing and to determine the final dissolution specifications at one year.

Product Name

The Sponsor proposed the trade name Cyclessa™ to replace the previously submitted IND drug name, CTR 77. This was submitted to the Labeling and Nomenclature Committee for review on 06/11/99 and approved 8/11/99.

Preclinical Pharmacology and Toxicology

All preclinical toxicology was cross-referenced to NDA 20-071 (Desogen). Since the dose levels of both the desogestrel and ethinyl estradiol components of the CTR 77 formulation are either equal to or lower than that in the approved NDA, the reviewer found it to be acceptable from a pre-clinical point of view. The Pharmacology reviewer recommends approval of the NDA.

Biopharmaceutics

The Agency had indicated in a regulatory letter to the Sponsor dated November 4, 1994 that data to assess the bioavailability of the lowest and highest tablet strength of CTR 77 would be required for the NDA. Studies 92005 and 92006 were submitted to support the bioavailability of the lowest and highest strength, respectively. The Sponsor was informed that a waiver of a bioavailability study for the intermediate tablet strength might be granted provided the Sponsor provides comparative *in vitro* dissolution profile data which demonstrates that the intermediate tablet strength dissolution profiles are similar to those of the lowest and highest tablet strengths of CTR 77. The Sponsor has requested a waiver for bioavailability of the intermediate strength. In addition, it was communicated to the Sponsor that a multiple dose study for CTR 77 is needed to demonstrate steady state serum/plasma drug (or metabolite) profiles for each tablet strength utilizing the 7/7/7-type sequential dosing regimen in CTR 77. Finally, although there are differences between the to-be-marketed and clinical trial formulations, the Sponsor is requesting a bioequivalence waiver.

Studies 92005 and 92006 assessed the bioavailability of the lowest and highest tablet strengths relative to a combination desogestrel/ethinyl estradiol oral solution. In general the mean relative bioavailability was greater than 95% for both studies. The request for a bioavailability waiver of the intermediate strength and the bioequivalence waiver for the difference in the to-be- marketed and the clinical trial formulation were addressed by comparison of the *in vitro* dissolution profiles. Following review of the submitted *in vitro* dissolution comparison data, the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II) has granted the request for waiver of the intermediate dose relative bioavailability study and the bioequivalence waiver. This Office finds that the NDA is acceptable for approval. OCPB/DPEII has recommended that the Sponsor tighten the *in vitro* dissolution specifications to not less than — Q) of the labeled amount dissolved in 15 minutes. This was communicated to the Sponsor and accepted as previously noted. OCPB/DPEII recommendations for the Clinical Pharmacology and Precautions sections of the label have been communicated to the Sponsor.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

In addition to the Fiddes site which was excluded by both the Sponsor and the FDA, there was a second site of concern. The evaluative report of the clinical inspections for NDA 21-090 noted that clinical site #12 (in Protocol 92-002, Dr. Fordyce) was not acceptable.

The report noted that clinical visit data were recorded for subjects when in fact these subjects had not been in clinic. The recommendation from the DSI reviewer was that data from this clinical site not be used.

Clinical Efficacy

Contraceptive efficacy
Contraceptive efficacy was studied in two Phase 3 trials in which 2768 subjects were exposed to CTR 77 for a total of 14,527 cycles and 2784 subjects were exposed to Ortho-Novum 7/7/7 for a total of 14, 758 cycles. Of the total CTR 77 and Ortho Novum 7/7/7 subjects exposed, 35.6% were starters and 64.4 % were switchers. The Sponsor's intent-to-treat analysis excluded the Fiddes site (at which no pregnancies occurred) and included 2,643 subjects in the CTR 77group who were exposed for 14,456 cycles and 2675 subjects in the ON 7/7/7 group who were exposed for 14,674 cycles. There were 12 "In-treatment" pregnancies included in the Sponsor's Intent-to-Treat analyses .The Pearl Index for CTR 77 using the Intent-to-Treat analysis was 1.08 per 100 women years. The pregnancy odds ratio of CTR 77 versus ON 7/7/7 from the Intent-to-Treat analysis was 1.351 with an upper bounds of the two-sided 95% confidence interval of 2.794. The six cycle Life-Table cumulative pregnancy rate for CTR 77 is estimated as 0.0051.

No pregnancies were conceived in trial subjects participating at Site 64 with principle investigator Fiddes. Because there were only 14 CTR 77 subjects (with 71 cycles of use) at that site, calculations of the Pearl Index, pregnancy odds ratio and life table analysis which included the data from the Fiddes site would not have been substantially different. Site 4 (Fordyce) had one "In-Treatment" pregnancy in 47 subjects treated for 258 cycles. Exclusion of this data would give a lower Pearl Index than that indicated above.

The Sponsor's definition of "In-treatment pregnancies" included those pregnancies conceived from the start of pill use through the last pill use (according to the MO reviewer this could include last pill use of placebo). Because of the inherent limitations in determination of the estimated date of conception (the best estimate being that made from 1st trimester Crown Rump Length [CRL] ±6-7 days with progressively less accuracy from later ultrasound measurements and other laboratory and physical determinations of pregnancy), this reviewer believes that it is appropriate to consider pregnancies occurring within 14 days of last active pill use as "In-treatment" pregnancies. The statistical reviewer was asked to consider this in her review. The Intent –to-treat analyses, including pregnancies occurring within 14 days of discontinuation of study drug (which might have been for some cases 21 days after the active drug), had a Pearl Index and Life Table 6 months pregnancy rate which were essentially unchanged from the Sponsors-Intent-to-Treat analysis.

The Clinical reviewing team has determined that CTR77 is efficacious in pregnancy prevention.

The review of the Sponsor's Cycle Control analysis of CTR 77 (analysis of patterns of intermenstrual bleeding, breakthrough bleeding and spotting and the absence of withdrawal bleeding) demonstrated that the formulation has acceptable cycle control.

Clinical Safety

The All-Subjects-Treated pooled safety data for CTR 77 included 2,768 subjects with 14,527 cycles of exposure. There was one accidental death (drowning following a scuba-diving accident) in a subject treated with CTR 77. There were no myocardial infarctions or strokes. There were three serious adverse events in CTR 77-treated subjects. Of these, there was one vascular disorder, a carotid artery aneurysm, in a 36 year old subject who had visual symptoms prior to enrollment in the study. The second serious adverse event was a cholecystitis in a 28 year old. The third serious adverse event was a venous thromboembolic event (VTE). This was a deep venous thrombosis in a 38 year old non-smoker.

It was the conclusion of the 1997 WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives that "combined oral contraceptive preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to combined oral contraceptives containing levonorgestrel". While the Division remains cognizant of this concern and has included language in the warnings section of desogestrel-containing oral contraceptives reflecting this concern, it has determined that Desogen, Ortho Cept, and Mircette, all desogestrel-containing OCs are safe and effective for use. There are no gestodene-containing products approved for use in the US. The Division continues to monitor the published literature for new data relating to the risk for VTE associated with Desogestrel-containing OCs (and gestodene-containing OCs that are approved in other countries).

The point estimates (and upper limits of the two-sided 95% Confidence Intervals) of the rates of VTE in women on CTR 77expressed as per 1000 subjects treated and per 100,000 women years of exposure are 0.36 (2.0) and 90 (499), respectively. These rates of VTE among the Cyclessa-treated women are not unusual when compared with the results from the other approved desogestrel-containing oral contraceptives (Desogen-0.84/1000subjects [4.7] and 114/100,000 women years [634], Mircette-0.00/1000 subjects [3.0] and 0/100,000 women years [341]. The Clinical Review has determined that CTR 77 is safe for use.

Conclusions and Recommendations

Cyclessa, CTR 77, is safe and effective for use and it is recommended that this NDA be approved.

Label

Major points of the labeling discussions included changes to the CLINICAL PHARMACOLOGY and PRECAUTIONS on disposition of CTR 77 in hepatic insufficiency and changes to PRECAUTIONS on DRUG INTERACTIONS. Under WARNINGS-THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS-a. Thromboembolism, the following paragraph describing the small increase in risk for VTE has been underlined to read:

[redacted]

[redacted] The highlighting of this statement would be applied to all desogestrel-containing oral contraceptives labels.

In a teleconference of 3/2/00 the Sponsor indicated that they were not prepared to accept the labeling changes as proposed and that they would not be sending in a label before the action date. Therefore, the NDA will receive an approvable action pending resolution of the label.

/S/ 3/7/00

Shelley R. Slaughter, M.D, Ph.D.
Reproductive Medical Team Leader

cc: NDA 21-090,
HFD-580/S. Allen/ M. Mann/ S. Slaughter/ D. Davis/ J. Mercier,

APPEARS THIS WAY
ON ORIGINAL

DEC 1 8 2000

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Sponsor's Response to Approvable Letter

NDA: 21-090 Cyclessa™

Major Amendment:

Submitted: 10/19/00
CDER stamp: 10/20/00
MOR completed: 12/12/00

Original Dates:

Submitted: 5/07/99
CDER stamp: 5/10/99
CDER due date: 3/10/00
MOR completed: 3/07/00

Key words: contraception (hormonal), CTR 77, Cyclessa, desogestrel, ethinyl estradiol, oral contraception

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:

Generic: desogestrel and ethinyl estradiol
Code: CTR 77
Trade: Cyclessa
Chemical: desogestrel chemical names:
(17α)-13-ethyl-11-methylene-18,-19-dinor-pregn-4-en-20-yn-17-ol, or
17α-ethynyl-18-methyl-11-methylene-Δ^4-estren-17β-ol
ethinyl estradiol chemical names:
(17α)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, or
17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Oral
Dosage form: Tablet
Strength:

Days 1-7:	(7 days)	100 mcg desogestrel + 25 mcg ethinyl estradiol
Days 8-14:	(7days)	125 mcg desogestrel + 25 mcg ethinyl estradiol
Days 15-21:	(7 days)	150 mcg desogestrel + 25 mcg ethinyl estradiol
Days 22-28:	(7 days)	placebo

Proposed indication: Oral contraception

Related NDAs:

NDA 20-071 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product - Organon Inc.

NDA 20-301 CTR 04 - Ortho-Cept 21 and 28 (desogestrel and ethinyl estradiol) Tablets - marketed product - R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ

NDA 20-713 CTR 25 – Mircette® (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets - marketed product - Organon Inc.

Safety Update:

The sponsor submitted a safety update on November 1, 2000, stating that there are no further adverse events to report and that the product has not yet been marketed anywhere in the world. Therefore, there are no additional safety concerns for Cyclessa (CTR 77) other than the major issue of the increased incidence of VTEs associated with third generation OCs, as discussed at length in the previous medical officer review of this NDA dated 3/07/00.

Labeling Review:

The current submission received on 10/20/00 consisted of a revised draft label from the sponsor. The proposed label contains the basic information and format found in the guidance document for class labeling for oral contraceptives. The current label was thoroughly reviewed and contains all the changes that the Division required of the same sponsor concerning the Mircette® label and the approximate 2-fold increased risk of venous thromboembolism with third generation OCs, including those containing desogestrel [the progestin in Mircette® and Cyclessa™], compared with certain second generation OCs.

The label does not contain any specific clinical efficacy data from the two large, randomized, comparative, six-month clinical trials. Although pregnancy is a definitive, easily measured endpoint, the difficulty with including data from the two trials in the final printed label (FPL) is that contraceptive clinical trials included in past NDA submissions differ in several respects:

- Length of product use in the trial(s): 6-12 months
- Comparative vs. non-comparative trial design
  - Choice of the active comparator if one is used
- Age range of trial subjects: inclusion criteria cut off at 35, 38, 40, 45, 50 years of age
- Number of cumulative years of product use
- Accuracy of determining date of conception and calculating product failure rates
- Per protocol [perfect] use vs. Typical [actual] use
  - Different definitions for per protocol use patient populations

Cyclessa has an acceptable Pearl Index (pregnancies per 100 women-years of use) and cycle control pattern, but such specific data in the FPL should not be included. This will avoid the issue of misleading or unsubstantiated comparative marketing claims. Likewise,

This table cannot be included in the final label because the trial was not designed to show such a difference, and because the sponsor has added all the subjects together to show mean average changes by treatment group [Cyclessa™ vs. OCs comparator], rather than individual subject's or percentile changes, or a range of changes.

Recommended changes to the original label also provide clinical pharmacology (PK and PD) information relative to liver function and address drug/drug interactions that may reduce the contraceptive effectiveness of Cyclessa™ or change the serum levels of the active progestin and estrogen.

Another recommended change made throughout the label involves the statement concerning using another method of birth control, "such as condoms, " as a contraceptive back-up when indicated. There is no sponge product currently on the market and foam is only one formulation of currently available spermicides in the United States. It is therefore recommended that this phrasing be changed to "condoms, spermicides, , or diaphragm" throughout the final label.

All other changes in the original label were minor in nature and are not outlined or discussed here.

/S/ 12/18/00

Daniel Davis, M.D.
Medical Officer, HFD-580
DRUDP

Date

/S/ MD 12/15

Dena Hixon, M.D.
Team Leader, DRUDP

cc: Daniel Davis, M.D.
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Susan Allen, M.D.
Jila Boal, Ph.D.
Jennifer Mercier, B.S.
NDA 21-090 and 21-091
Division file
DFS: to be electronically submitted by the medical officer

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APPEARS THIS WAY
ON ORIGINAL

MAR 7 2000

HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review

NDA: 21-090 Cyclessa

Date submitted: 5/07/99
CDER stamp: 5/10/99
CDER due date: 3/10/00
MOR completed: 3/07/00
Key words: contraception, CTR 77, Cyclessa, desogestrel, ethinyl estradiol, oral contraception

Sponsor: Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Drug names:

Generic: desogestrel and ethinyl estradiol
Code: CTR 77
Trade: Cyclessa
Chemical: desogestrel chemical names:
(17α)-13-ethyl-11-methylene-18,-19-dinor-pregn-4-en-20-yn-17-ol, or
17α-ethynyl-18-methyl-11-methylene-Δ^4-estren-17β-ol
ethinyl estradiol chemical names:
(17α)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, or
17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol

Drug class: Progestin and estrogen (steroids)
Route of administration: Oral
Dosage form: Tablet
Strength:

Days 1-7:	(7 days)	100 mcg desogestrel + 25 mcg ethinyl estradiol
Days 8-14:	(7days)	125 mcg desogestrel + 25 mcg ethinyl estradiol
Days 15-21:	(7 days)	150 mcg desogestrel + 25 mcg ethinyl estradiol
Days 22-28:	(7 days)	placebo

Proposed indication: Oral contraception

Related INDs:

IND 32,483 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product-Organon Inc.

IND 43,289 CTR 25 - Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets- marketed product-Organon Inc.

IND 45,548 CTR 77/ Cyclessa/ (desogestrel and ethinyl estradiol) Tablets-Organon Inc.

Related NDAs:

NDA 20-071 CTR 04 - Desogen® (desogestrel and ethinyl estradiol) Tablets - marketed product - Organon Inc.

NDA 20-301 CTR 04 - Ortho-Cept 21 and 28 (desogestrel and ethinyl estradiol) Tablets - marketed product - R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ

NDA 20-713 CTR 25 - Mircette™ (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets - marketed product - Organon Inc.

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1.0 RESUME

Exposure to first or second generation oral contraceptives containing the synthetic progestins levonorgestrel or norethindrone has been associated with androgen-dependent clinical and metabolic adverse effects. Oral contraceptives containing androgenic progestins induce changes in lipid/lipoprotein patterns that are considered undesirable in view of the epidemiological association of such changes with increased risk of coronary artery disease. In addition, androgenic progestins have been associated with adverse effects in users, such as weight gain and acne. Third generation oral contraceptives containing the newer progestins, desogestrel (DSG) or gestodene, were developed to obtain a higher ratio between the desired progestational effects and the undesired androgenic effects.

This submission (CTR 77) and [redacted] are for two third generation triphasic oral contraceptives. Both products contain the combination of ethinyl estradiol and desogestrel as does the monophasic Desogen and biphasic Mircette, which are already on the U.S. market. CTR 77 provides a 7/7/7 triphasic regimen of 100 mcg DSG on days 1-7, 125 mcg of DSG on days 8-14 and 150 mcg DSG on days 15-21, while Desogen and Mircette each contain 150 mcg DSG on days 1-21. CTR 77 contains a constant low dose of 25 mcg ethinyl estradiol (EE) on days 1-21, while Desogen contains 30 mcg EE on days 1-21 and Mircette contains 20 mcg EE on days 1-21 and 10 mcg of EE on days 24-28. CTR 77 and Desogen contain placebo tablets on days 22-28, while Mircette contains placebo tablets only on days 22-23. The aim of the CTR 77 regimen is to maintain contraceptive efficacy and a regular pattern of menstrual bleeding despite a reduction in the dose of EE (compared to Desogen) and a reduction in the overall progestin dose. Dose selection was empirically based on previous clinical trials.

Compared to Mircette (and Desogen), CTR 77 reduces the total DSG dose per cycle by ~17%. To address the theoretical concern that lowering the total desogestrel dose could lead to poorer efficacy and cycle control, the sponsor increased the ethinyl estradiol dose to 25 mcg/day as compared to Mircette's 20 mcg/day. Other marketed triphasic oral contraceptives, such as Ortho-Novum 7/7/7 (ON 7/7/7), contain 35 mcg EE on days 1-21. CTR 77 has 29% lower total EE dose per cycle (525 mcg) compared to ON 7/7/7 (735 mcg total) and 17% lower total EE dose per cycle compared to Desogen (630 mcg total).

The submission from Organon Inc. includes two Phase 3 U.S. studies 092001 and 092002, each designed to accumulate information about the contraceptive efficacy, vaginal bleeding patterns, and safety of both the CTR 77 and 99 regimens in women who elected to use oral contraception for the prevention of pregnancy.

Each study was a multicenter, randomized, open-label, comparative, efficacy and safety study of CTR 77, CTR 99, and ON 7/7/7. Study 092001 was conducted in 65 centers in the United States and study 092002 was conducted in 67 centers in the United States. **The data from these two controlled clinical studies have been pooled for analysis in this review since these studies were identical in design.** Following completion of the clinical studies, one of the principal investigators for study 092002, Dr. Robert Fiddes (Site 64/092002), was charged and subsequently convicted of falsifying data in drug studies for several pharmaceutical companies. Since the integrity and validity of the study data from Dr. Fiddes' site could not be verified, the data from this site have been excluded from all efficacy analyses. For the purposes of full disclosure, Dr. Fiddes' data are included in the demographic data and in the Integrated Summary of Safety (ISS). In their Appendix B, the Sponsor separately presented pooled safety data with Site 64/092002 excluded, and the data for Site 64/092002 only.

> **Reviewer comment: Dr. Fiddes enrolled 14 subjects who completed 71 cycles on CTR 77 and 14 subjects who completed 78 cycles on Ortho Novum 7/7/7. It is appropriate to question the validity of the efficacy data and thus exclude it from all efficacy analyses. In the interest of full disclosure, the Sponsor has included data from the Fiddes site in the Integrated Summary of Safety. Because it is not possible to determine whether AEs were underreported, we can only accept the data that were reported. It would be entirely speculative to discuss the impact of non-reported AEs, but it is theoretically possible that they might have had an influence on the outcome of this review.**

The sponsor was unaware, however, of any problems with Dr. Fordyce's data (Site 12, Study 002), so they did not exclude this data from their efficacy or safety analyses. Three subjects had recorded data on dates when they were not in the clinic. Our DSI recommendation [final review from DSI reviewer dated 2/28/2000] is to exclude all data from this site, which enrolled 47 CTR 77 subjects with 258 cycles of exposure and 46 ON 7/7/7 subjects with 259 cycles of exposure. There was one during-treatment pregnancy reported at this site. Later reviewer comments will analyze the efficacy (Pearl Index) with and without the data from Site 12. The sponsor and medical officer safety analyses include the data from Dr. Fordyce's site.

At least half the subjects in each center were expected to be **Starters (defined as no OC use in the two months immediately preceding study entry)** and the remaining subjects were to be Switchers from other combined OCs. In the All Subjects Treated Group (2,768 on CTR 77 and 2,784 on Ortho-Novum 7/7/7), **35.6% were Starters and 64.4% were Switchers**. The women had to meet the entry criteria for enrollment. Women were followed every three months for 6 cycles. Endpoints included contraceptive efficacy, bleeding patterns (cycle control), and safety.

Reviewer comment: there is no standard definition of starters and switchers in other OCs trials that have recently been reviewed by the FDA. Approximately 6% of the subjects in the trials had never used OCs at any time prior to the trial; all others were "switchers" or prior OCs users.

2.0 BACKGROUND

OCs are divided into three generations:

1. First generation: high dose OCs with greater than 50 mcg estrogens (Enovid in 1960 contained 150 mcg mestranol and 9.85 mg norethynodrel) were first developed.
2. Second generation: in the1970s, the dose-response relationship between adverse events and the amount of steroids in the pill was appreciated and "low dose" OCs with norethindrone and levonorgestrel (LNG) were developed.
3. Third generation: in the 1980s, the androgenic metabolic effects especially in terms of cardiovascular disease were recognized and low dose estrogen OCs with new progesterone components (gestodene, desogestrel, or norgestimate) were introduced. The term "third generation" progestin derives from the fact that they appeared on the market at roughly the same time rather than from any pharmacological resemblance.

The progestin component of CTR 77 is desogestrel, a third generation progestin. Based on animal and human studies, it has high progestational activity, no estrogenic activity and only weak androgenic activity, making it less likely than some other progestins to cause unfavorable effects on lipids. Organon Inc. in Oss, the Netherlands, discovered Desogestrel in the early 1970's. Organon Inc. began clinical development of a monophasic OC containing 150 mcg DSG in combination with 30 mcg EE (CTR 04) in Europe. In 1981 West Germany was the first country to approve CTR 04 for the market (under the trade name of Marvelon®). In the United States since early 1993, CTR 04 has been marketed as Desogen® by Organon Inc. and as Ortho-Cept® by Ortho Pharmaceutical Corporation. Currently on the USA market, there are two OC formulations (CTR 04 and CTR 25) and three brand name OCs (Desogen, Ortho-Cept, and Mircette) containing desogestrel. Outside the USA market, there are currently five desogestrel-containing OC formulations approved for marketing (see Table #1 on next page).

Table #1-**Formulation of Desogestrel (DSG)-containing OCs**

Brand name	**Approved**	**days 1-21**	**days 22-23**	**days 24-28**
Desogen **Ortho-Cept** **(both CTR 04)**	**12/10/92** **12/14/92** **USA**	DSG 150/EE 30	placebo	
Mircette (CTR 25)	**USA** **4/22/98**	DSG 150/EE 20	placebo	EE 10
Gracial (22 day)	Outside USA	DSG 25/EE 40 (D#1-7) DSG 125/EE30 (D#8-22)	no placebo (D#23-28)	
Marvelon (CTR 04) (21 and 28 day)	Outside USA	DSG 150/EE 30	Marvelon 28-placebo; Marvelon 21-no placebo	
Mercilon (21 & 28 day)	Outside USA	DSG 150/EE 20	Mercilon 28-placebo; Mercilon 21-no placebo	
Ovidol (22 day)	Outside USA	EE 5 (D#1-7) DSG 125/EE 50 (D#8-22)	no placebo (D#23-28)	
[redacted]				
CTR 77 (Cyclessa)	**Pending** **NDA 21090**	**DSG 100/EE 25 (D#1-7)** **DSG 125/EE 25 (D#8-14)** **DSG 150/EE 25 (D#15-21)**	placebo	
[redacted]				

Reviewer comment:
It appears that the sponsor is trying to achieve with CTR 77 a formulation that has a lower estrogen and progestin dose than does the monophasic Desogen formulation. The desired advantage is a lower cardiovascular risk while maintaining efficacy and cycle control. The CTR 77 formulation contains a 17% lower total cycle dose of DSG compared to Desogen and Mircette (see Table #2). However, to maintain cycle control with the lowered DSG formulation, the Sponsor elected to use a total EE cycle dose of 525 mcg (higher than the biphasic Mircette, but lower than the monophasic Desogen).

Table #2-**Total Cycle DSG and EE Content of DSG-Containing OCs**

Brand name	Total Cycle Dose DSG (in descending order)	Total Cycle Dose EE
Desogen®/Marvelon®/Ortho-Cept®	3150 mcg	630 mcg
Mircette™	3150 mcg	470 mcg
Mercilon	3150 mcg	420 mcg
CTR 77	**2625 mcg**	**525 mcg**
[redacted]	[redacted]	[redacted]
Gracial	2050 mcg	730 mcg
Ovidol	1875 mcg	785 mcg

Increased risk of venous thromboembolism (VTE):

Late in 1995, epidemiology reports were published linking combined oral contraceptives (COCs) containing desogestrel and gestodene with venous thromboembolism (VTE). VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). The WHO Study[1] (21 centers in 17 countries) matched controls to cases within 5-year age bands. This study found an Odds Ratio (OR) of 2.4 (CI 1.3-4.6) or a 2.4:1 increase in VTEs in COC users containing third generation progestins compared to first or second-generation progestins. The Transnational Study[2] used a protocol similar to that of the WHO study, but was specifically designed to compare the cardiovascular risks of combined OCs containing different progestagens matched within 5-year age bands. The Transnational Study reported an OR of 1.5 (CI 1.1-2.2) or a 1.5:1 increase in VTEs when comparing DSG to LNG users. The Boston Collaborative Study[3] investigated the risks of cardiovascular death and nonfatal VTE among women who used different OCs through the General Practice Research Data Base of over 4 million people in the UK. Here the adjusted matched relative risk from a nested case-control analysis was 2.2 (CI 1.1-4.4) or a 2.2:1 increase in VTE when comparing DSG to LNG users.

Table #3-**VTE and OCs: Study Descriptions and Main Results**[4]

Study	WHO[1]	Transnational[2]	Boston Collaborative[3]
Design	Case-Control	Case-control	Cohort
No. of centers	21 in 17 countries	10 in Germany and UK	370 general practices in UK
Cases/controls (n)	1143/2998	471/1772	75/300*
Odds Ratio (95% CI) DSG vs. LNG	2.4 (1.3-4.6)	1.5 (1.1-2.2)**	2.2 (1.1-4.4)

*nested case-control subgroup analysis

**compared with OCs containing all progestins other than DSG or GSD

1 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, effects of different progestagens in low estrogen OCs on venous thrombolic disease. *Lancet* 1995; 346: p. 1582-88.

2 Spitzer WO et al., Third generation oral contraceptives and risk of thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: p. 83-88.

3 Jick H et al., Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; 346: p. 1589-93.

4 Ory H, Epidemiology of Venous Thromboembolic Disease and OC Use. *Dialogues in Contraception* Fall 1996; Vol. 5, No. 1, p. 4.

On October 18, 1995, in response to the unpublished WHO, Transnational, and Boston Collaborative Drug Surveillance Program studies, **the United Kingdom (UK) Committee on Safety of Medicines (CSM) issued a warning advisory concerning OCs that contained DSG and GSD to all UK physicians:**

> For LNG-, norethisterone-[norethindrone], or ethynodiol-containing products "the excess risk of thromboembolism in users is around 5 to 10 cases per 100,000 women per annum" and "OCs containing DSG and GSD are associated with around a two-fold increase in the risk of thromboembolism compared with those containing other progestagens." "Women taking OCs that include DSG or GSD should be strongly urged to complete their current cycle." OCs that include DSG or GSD "should only be used by women who are: intolerant of other combined OCs and prepared to accept an increased risk of thromboembolism."

Some physicians interpreted this warning to mean that OCs containing DSG or GSD should not be prescribed, while others did not prescribe them as first line choices for women with no prior use of OCs, except occasionally to women with severe acne.

Additional Regulatory Agencies communications regarding OCs and nonfatal VTE soon followed:

- European Union's Committee for Proprietary Medicinal Products (CPMP)-Position Statement & CPMP Ad Hoc Expert Working Group Statement: (Oct. 27, 1995) "In view of its benefit/risk re-assessment, the CPMP did not consider it appropriate to withdraw combined OCs containing GSD or DSG." "[T]o date, there is no evidence to draw conclusions that the cardiovascular mortality is different for DSG- or GSD-containing combined OCs compared to LNG-containing combined OCs." Concerning the somewhat greater risk of VTE for DSG- or GSD-containing OCs compared to LNG-OCs it was stated: "there is no plausible biological explanation for the differences." "[T]he risk of VTE with all combined OCs is still substantially less than the risk of VTE in pregnancy."

- German Federal Institute for Drugs and Medical Devices (BfArM)-Press Release: (Nov. 6, 1995) "[C]ontraceptives with DSG and GSD cannot be prescribed to women under 30 years of age and using the pill for the first time." "For women who are happy with this pill and would like to continue with it, BfArM does not see any reason for them to change."

- FDA-Talk Paper: (Nov. 14, 1995) "FDA has concluded from its review of three recent unpublished studies that the risk is not great enough to justify switching to other products." " FDA will work with the manufacturers to update this information in the product's labeling. The agency, however, does not recommend that women using the DSG containing products stop using them or change to another OC."

Of 16 regulatory decisions reviewed by Dr. Michael Lewis, 3 agencies (in UK, Germany, and Norway) restricted the use of third-generation oral contraceptives, 6 issued warnings, and 7 (including the European agency) took no action.[5] With their publications, it was apparent that the above 3 studies with their subsequent publications showed the incidence of venous thromboembolism among women who used third generation OCs to be higher than that among women who used second-generation products. Subsequently, the interpretation of the results of the 3 studies has been criticized primarily for bias and confounding factors [causal relationship vs. selection bias].[6]

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5 Lewis M, The epidemiology of oral contraceptive use: A critical review of the studies on oral contraceptives and the health of young women. *Am J Obstet Gynecol* Oct. 1998: Vol. 179, No. 4, p.1096-97.

6 Lidegaard O and Milson I, Oral contraceptives and Thrombotic Diseases: Impact of new epidemiological studies. *Contraception* 1996; 53: p. 135-39.

In November 1997, The World Health Organization convened a meeting of scientific experts to consider the safety of the new progestins. They concluded that, "COC preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to COC containing levonorgestrel. There are insufficient data to draw conclusions with regard to COC containing norgestimate." In addition, the group concluded, "The suggestion that gestodene- or desogestrel-containing low dose COC may carry a lower risk of myocardial infarction compared with low dose formulations containing levonorgestrel remains to be substantiated."[7] On December 19, 1997, the German ban was lifted.

In February 1999, Burnhill assessed the risk of thromboembolic events in 2,265,087 woman-years of OCs use in a group of Planned Parenthood Federation of America patients and found a statistically significant increase in the relative risk of pulmonary emboli in desogestrel users compared to norgestimate or norethindrone OC users.[8] In July 1999, Herings reported new use of third generation oral contraceptives was associated with a four-fold increased risk of VTE compared with users of second generation oral contraceptives, particularly among young, healthy women.[9] He had examined data from the PHARMO system, which included information of hospital admissions and drug-dispensing for all 450,000 residents of eight Dutch cities, to identify exclusive use of second or third generation oral contraceptives among new users. Bloemenkamp offered the biological explanation for the differences to be an interaction between types of oral contraceptives and an unidentified susceptibility factor that might be a prothrombotic mutation, such as factor V Leiden mutation.[10] In September 1999, Mellemkjaer reported a 16% increase in admission rates for VTE in a population study from Denmark which correlated with the increase in prescription of third generation contraceptives.[11]

2.1 Regulatory history

CTR 04 (Desogen and Ortho-Cept in USA, Marvelon outside USA)
This monophasic formulation contains 150 mcg desogestrel and 30 mcg ethinyl estradiol in a 21 day regimen. It was submitted on 12/15/88 as IND 32,483 by Organon Inc. The NDA 20-071 for CTR-04 (Desogen) was submitted by Organon Inc. on 12/31/90 and was approved on 12/10/92. The Pearl index was 1.14, which was felt to be somewhat high but acceptable. Headaches and dysmenorrhea were more frequent than in other OC studies, but this was felt to be the result of ascertainment bias. On 10/8/92, Organon Inc. granted authorization for the agency to refer to the then pending NDA 20-071 for Desogen on behalf of The R.W. Johnson Pharmaceutical Research Institute. The NDA 20-301 for CTR-04 (Ortho-Cept) was submitted by The R.W. Johnson Pharmaceutical Research Institute on 10/8/92 and was approved on 12/14/92.

[redacted]

7 WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, Report of a WHO scientific group. *WHO Tech Rep Ser* 1998; No. 877.
8 Burnhill MS, The use of a large-scale surveillance system in Planned Parenthood Federation of America clinics to monitor cardiovascular events in users of combination oral contraceptives. *Int J Fertil Womens Med* 1999 Jan-Feb; 44 (1): p. 19-30.
9 Herings R et al., Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.
10 Bloemenkamp K et al., Venous thromboembolism and oral contraceptives. (Letter), *Lancet* 1999; 354: p. 1469.
11 Mellemkjaer L et al., Admission for and mortality from primary venous thromboembolism in women of fertile age in Denmark, 1977-95. *BJM* 1999; 319: p. 820-21.

CTR 25 (Mircette)
This biphasic formulation contains 150 mcg desogestrel and 20 mcg ethinyl estradiol for days 1-21, placebo for days 22-23, and ethinyl estradiol for days 24-28. Organon Inc. submitted CTR 25 as IND 43,289 on 8/26/93. NDA 20-713 for CTR 25 was submitted by Organon Inc. on 4/30/97 and approved on 04/22/98. The NDA included an open label non-comparative study of 1226 women at 33 sites in the U.S. for up to 18 cycles, with 327 women completing 13 cycles. The endpoints were efficacy, bleeding, and safety. The Pearl Index for this product using all 14,050 cycles of exposure was 1.11 pregnancies per 100 woman-years. The life table rate for the first 13 cycles of use was also 1.11. The pattern of AE was consistent with that seen with other OCs and did not raise safety concerns.

The NDA included seven sub-studies that evaluated lipid profiles, endocrine effects, endometrial histology, carbohydrate metabolism, steady state pharmacokinetics, hemostasis/ fibrinolysis, and ophthalmic conditions.

The sponsor agreed to comply with a Phase 4 commitment noted in the NDA approval letter "to perform a clinical study to assess the risk of endometrial hyperplasia in women after one year of therapy," and to submit the study results by 4/22/01. Organon submitted a draft proposal of this Phase 4 study, Protocol 086007, on May 12, 1999. This submission (N-038) included plans to enroll 80 subjects in order to achieve 40 women completing the trial by February 2001.

CTR 77 (Cyclessa)
This triphasic formulation contains 100/125/150 mcg desogestrel and 25/25/25 mcg ethinyl estradiol in a 7/7/7 day regime. It was originally submitted as [redacted] and was transferred to Organon Inc. on 9/1/98. Organon Inc. also submitted CTR 77 as IND 45,548 for both CTR 77 a[redacted] Tablets (desogestrel and ethinyl estradiol) on 6/21/94. The MO review was completed on 7/19/94 for the two identical trials that were carried out for this NDA submission. From this review, "efficacy data collected on the 3 arms under the 2 protocols are intended to be pooled.

The objective of the analysis of the pooled data is to compare contraceptive efficacy of CTR 77 and CTR 99 with that of Ortho Novum 7/7/7 using at least 10,000 evaluable cycles of exposure to each drug." On 9/42/94 it was agreed that CTR 77 steady state pharmacokinetics must be assessed at all strengths of the regimen and that bioavailability requirements for the highest and lowest doses cannot be waived.

On 5/16/95, a Pre-NDA clinical meeting was held to discuss the following for CTR 77 [redacted]

- inclusion/exclusion criteria for both the 092-001 and 092-002 safety and efficacy 3-arm studies initiated in July 1994
- statistical considerations
- composition of the NDA

In July 1995 enrollment was completed for both studies and the sponsor stated that they intended to file the 2 NDAs in the fourth quarter of 1996. On 5/18/98, a pre-NDA clinical teleconference was held with the Division of Reproductive and Urologic Drug Products (HFD-580) to review the prior agreements of the 5/16/95 clinical meeting and to discuss additional proposals with respect to the format and content of the clinical sections of the NDA, such as the electronic submission of Case Report Forms and Case Report Tabulations. It was agreed that the data from Dr, Fiddes' site # 64 in study 002 would be excluded from the ISE analysis and reported separately as an addendum to the ISE. For purposes of full disclosure, Dr Fiddes' data would be included in the ISS. HFD-580 agreed to honor previous agreements as well as accept the additional proposals.

The agency received NDA 21-090 for CTR 77 from Organon Inc. on May 7, 1999.

2.2 Preclinical studies

All preclinical pharmacology, toxicology, tumorigenicity, reproductive toxicology, postnatal development, mutagenicity studies as well as pharmacokinetics were conducted under sponsor's IND 32,483 for CTR-04 and IND [redacted] The non-clinical section of this NDA is included by cross-reference to the non-clinical sections of Desogen (CTR 04) NDA 20-071 (IND 32,483) and [redacted]

2.3 Human pharmacology studies

The following U.S. Clinical Pharmacology studies were conducted for CTR 77:

#092-004: *"An Open Label, Single Center, Pharmacokinetic Study of a Triphasic Combination Oral Contraceptive, CTR 77"*
Twenty-four healthy female volunteers were enrolled in this U.S. study between June 1995 and December 1995 to determine whether:

- steady state was reached for etonogestrel (active metabolite of DSG) and EE within each dosing phase,
- etonogestrel steady state serum concentrations were proportional to the DSG dose during Cycle 3 of CTR 77 treatment,
- EE steady state levels were similar under different co-administered DSG doses during Cycle 3 of CTR 77 treatment.

The study design was Phase 1, open label, multidose, randomized, non-comparative, and single center. The number of treatment cycles was 3. The racial distribution was Caucasian 83%, Black 8% (2/24), Asian 4%, and other 4%. The goal of 18 subjects completing the study was achieved (21 subjects completed the study and 3 were dropped).

#092-005 and 006 (identical studies): *"An Open Label, Single Dose, Two-Way, Crossover Bioavailability Study of CTR 77 Tablets and Solution"*
Twenty-four healthy volunteers were enrolled in each single-center U.S. study between June and September 1995 to determine the bioavailability of the active metabolites in a CRT 77 tablet relative to a solution containing the same amount of active metabolites. A single dose (2 tablets or 2 solution aliquots) was given in each of two consecutive cycles. Twenty-two of 24 women (mean age 34.8 and 31.4 years) completed each study.

Reviewer's comments:
Please see separate biopharm review for further details and analysis.

2.4 International marketing experience

CTR-04 (monophasic 150 mcg DSG/30 mcg EE) was first approved on February 10, 1981, in Germany as Marvelon®. It has been approved in a total of 103 countries. In the United States, CTR-04 is marketed as Desogen® by Organon Inc. and as Ortho-Cept® by Ortho Pharmaceutical Corporation.

Ovidol (5 mcg EE on days 1-7 and 125 mcg DSG/50 mcg EE on days 8-22) was first approved in Germany on February 10, 1981. It has been approved in a total of 5 European countries.

Mercilon (monophasic 150 mcg DSG/20 mcg EE) was first approved in Great Britain in 1986. It has been approved in a total of 54 countries.

Gracial (biphasic 25 mcg DSG /40mcg EE on days 1-7 and 125 mcg DSG/30 mcg EE on days 8-22) was first approved in Belgium in 1988. It has been approved in a total of 21 countries.

CTR-05 (triphasic 50 mcg DSG/35 mcg EE on days 1-7, 100 mcg DSG/30 mcg EE on days 8-14, and 150 mcg DSG/30 mcg EE on days 15-21) was first approved in Sweden in 1995 as Trimiron. It has been approved in a total of 4 countries and has not yet been marketed.

CTR-25 (biphasic 150 mcg DSG/20 mcg EE on days 1-21, placebo on days 22-23, and 10 mcg EE on days 24-28) has been approved only in the United States in January 1998 as Mircette™.

3.0 SUMMARY OF NDA CLINICAL SECTION

3.1 Summary of uncontrolled trials
There were no uncontrolled clinical trials submitted in this NDA.

3.2 Summary of controlled trials
There were two large Phase 3 trials submitted in this NDA: Protocol 092001 and 092002. The first subject was enrolled in Protocol 092001 on September 3, 1994, the last subject completed the study on December 12, 1995, and the Final Clinical Report was signed in September 1997. The first subject was enrolled in Protocol 092002 on September 15, 1994, the last subject completed the study on February 20, 1996, and the Final Clinical Report was signed in February 1998. Both trials were randomized, comparative, multi-center, open-label, parallel group, safety and efficacy studies of triphasic combination oral contraceptives, CTR 99 and CTR 77 versus Ortho-Novum 7/7/7, using a Sunday start regimen. **Identical protocols were used for both trials.**

Protocol 092001 enrolled a total of 4237 female subjects and treated (i.e. subject received at least one dose of study medication) a total of 4172 subjects. In the CTR 77 arm, 1392 subjects were treated in 7324 cycles. In the CTR 99

arm, 1387 subjects were treated in 7328 cycles. In the Ortho-Novum 7/7/7 arm, 1393 subjects were treated in 7375 cycles.

Protocol 092002 enrolled a total of 4238 female subjects and treated a total of 4156 subjects. In the CTR 77 arm, 1376 subjects were treated in 7203 cycles. In the CTR 99 arm, 1389 subjects were treated in 7192 cycles. In the Ortho-Novum 7/7/7 arm, 1391 subjects were treated in 7383 cycles.

The goal of a total of at least 10,000 evaluable cycles in each arm in a six-cycle treatment period was achieved. The studies were conducted for Organon Inc. by the [redacted]

4.0 PROTOCOLS 092001 and 092002:

OPEN-LABEL, RANDOMIZED, PARALLEL GROUP, COMPARATIVE, MULTICENTER, SAFETY AND EFFICACY STUDIES OF TRIPHASIC COMBINATION CONTRACEPTIVES CTR 99 AND CTR 77, VERSUS ORTHO-NOVUM® 7-7-7 (Vol. 49-68 for 001 and Vol. 69-90 for 002).

4.1 Objectives

The study objectives were to evaluate the safety, contraceptive efficacy, and cycle control of two triphasic DSG-containing combination OCs, CTR 99 and CTR 77, compared with a marketed triphasic norethindrone/EE combination OC (Ortho-Novum 7/7/7) using a Sunday-start regimen.

4.2 Design

Protocols 092001 and 092002 were open-label, randomized, parallel group, comparative, safety and efficacy studies conducted in 65 and 67 centers, respectively, in the United States. It was planned that half the subjects were to be Starters ("no OC use in the two months immediately preceding study entry") and half Switchers from other combined OCs.

> **Reviewer's comment:**
> **In the All Subjects CTR 77 treatment group, there were 36% Starters and 64% Switchers. Subjects switching from previous OCs use would be expected to have lower user-failure rates than subjects who were new starters. Switchers would also be expected to have a lower incidence of breakthrough bleeding. Both studies had an excess of switchers (64%) compared to starters (36%). However, the percentage of starters and switchers was balanced between all the treatment arms. It is interesting to note that only ~6% of the CTR 77 "starters" were first-time-ever OC users.**

4.3 Study population

A total of 8,475 female subjects were enrolled at 132 different centers in the 2 studies. The subjects were recruited between September 1994 and February 1996 from Obstetrics/Gynecology and/or Family Practices of the participating physicians or through advertisement. A total of 8,328 subjects received one of the three study medications (see Table #4).

Table #4-**092001/002 All Treated Subjects Groups**

CTR 99	2776 subjects	14,521 cycles
CTR 77	**2768 subjects**	**14,527 cycles**
Ortho-Novum 7/7/7	2784 subjects	14,758 cycles
Total #	**8,328**	**43,806**

4.3.1 Demographics

CTR 77 racial distribution was Caucasian 91.4%, Black 6.3%, Asian 1.2%, and Other 1.2%. Ortho-Novum 7/7/7 racial distribution was Caucasian 91.1%, Black 6.3%, Asian 1.6%, and Other 1.1%. The mean age was 28.4 years for the CTR 77 group and 28.5 years for the Ortho-Novum 7/7/7 group. Almost 85% of all subjects were between 20 and 39 years of age, while 6.7% were 18-19, and 8.3% were 40-50. The mean BMI of 23.8 kg/m^2 was identical in the CTR 77 and Ortho-Novum 7/7/7 subjects. An identical 51.4% of subjects in the CTR 77 and Ortho-Novum 7/7/7 were nulliparous. In the CTR 77 group, 81.3% did not smoke compared to 83.0% in the Ortho-Novum 7/7/7 group. The average mean coital frequency was not reported.

Reviewer's comment:
The two groups were well matched with regard to demographics and other baseline characteristics. As expected in a randomized clinical trial, there were no significant differences between the two arms. Over 90% of the subjects were Caucasian.

4.4 Inclusion and exclusion criteria: identical for both studies

Inclusion Criteria

1. Healthy woman, **within the age range of 18-50 years inclusive**, who were sexually active and at risk for pregnancy
2. Women who agreed to be available for study visits, were willing to use a Sunday-start OC regimen, and continue the study drug for six consecutive cycles
3. Women between 80-130% range of the ideal body weight
4. Women in whom pregnancy was ruled out before the start of the study
5. Women who were willing to give written informed consent to participate in the study
6. Women who were willing to complete the Confidential Follow-Up Form

Exclusion Criteria

1. Women for whom combination OCs were contraindicated
2. Women who had used an injectable hormonal contraceptive within the past six months, those who had used an intrauterine device (IUD) containing a progestogen for past three months, or had had a contraceptive implant removed within a period of two months prior to the Screening Visit
3. Women who were breast-feeding
4. Women who had not had three regular menstrual cycles following full-term pregnancy, abortion, or lactation
5. Women who required concomitant use (>21 consecutive days) of, or who had taken in the 30 days prior to enrollment, drugs known to interfere with the pharmacokinetics of OC. Included were: carbamazepine, phenytoin, primidone, hydantoins, barbiturates, or other hepatic enzyme-inducing drugs
6. Women who had ever been exposed to etretinate (Tegison®) and/or women who required concomitant use of isotretinoin (Accutane®) or had taken it within the 30-day period immediately prior to the Screening Visit
7. Women who were hypertensive (sitting diastolic blood pressure $\geq$ 90 mm Hg or systolic blood pressure $\geq$ 150 mm Hg)
8. Women who had any suspected or abnormal finding on pelvic or breast examination which, in the view of the investigator, precluded the woman from participating in the study
9. Women with evidence of significant cardiovascular, hepatic, or renal disease
10. Women with a history of (or current) parenteral insulin-treated diabetes or uncontrolled thyroid disorder
11. Women with a recent history of severe migraine headaches
12. Women with cycle lengths that were <21 days or >35 days within the past three months
13. Women who were currently consuming, on average, >2 drinks of an alcoholic beverages per day
14. Women who were $\geq$35 years old and heavy smokers ($\geq$ 15 cigarettes a day)

15. Women with a past (within 12 months) or current history of drug abuse (recreational, ethical, or over-the counter [OTC])
16. Any woman who had taken an investigational drug or used an investigational device within the past 90 days.
17. Women who had clinically significant abnormal findings on the screening laboratory assessments
18. Women with cervical Pap smear results reporting cellular changes associated with human papillomavirus (HPV), atypical glandular cells of undetermined significance (AGCUS), atypical squamous cells of undetermined significance (ASCUS) or more severe findings
19. Any woman, who in the judgement of the investigator, presented issues or concerns that may have confounded the reliability of compliance and information acquired in the study

Reviewer's comment:
The inclusion criteria "Healthy woman, within the age range of 18-50 years inclusive" differs from the majority of previous United States OC investigations, which have studied women in the age range of 18-35 (or 38) years inclusive. Accepting females until age 50 into the clinical trial potentially introduces the bias of decreased fertility due to age in certain subjects, especially women age 40-50. The value, however, is the information gained concerning efficacy and safety in women over 35. Numbers and percentages of all-subjects-treated treatment groups of CTR 77 and Ortho-Novum 7/7/7 were quite similar regarding the age groups 35-39 years, 40-44 years, and 45-50 years.

Table #5-**Age 35-50 Demographics by Treatment Group (All-subjects-treated Group)**

	CTR 77		Ortho-Novum 7/7/7	
	N	%	N	%
Age 35-39 years	346	12.5	307	11.0
Age 40-44 years	152	5.5	139	5.0
Age 45-50 years	35	1.3	36	1.3
TOTAL	533	19.3%	482	17.3%

4.5 Procedures

4.5.1 Screening period

The study design and purpose were explained at the Screen Visit, and the volunteers were assessed for eligibility. Written informed consent was obtained. The requirements of participation were thoroughly explained to the subject, including the use of home pregnancy test, compliance with back-up contraceptive methods (if used), returning used and unused tablet compacts, and availability for scheduled visits. A medical and gynecological history, pretrial medications (recreational, prescription and OTC) history, and the existence of any relevant pre-existing conditions were obtained. OC switchers were questioned regarding adverse experiences with their present OC. General characteristics including smoking, alcoholic beverage consumption and sexual activity were recorded. Vital signs and a complete physical examination (including breast, pelvic exam, and cervical Pap smear) were performed. Subjects had fasting blood drawn for serum pregnancy, chemistry and hematology testing. They also underwent dipstick urinalysis at the site, with a complete urinalysis sent to the central laboratory if the dipstick was found positive for protein, ketones, glucose, nitrite or blood. Starter subjects and switcher subjects not currently on an OC were instructed to use a back-up method prior to starting study drug and until the first seven active tablets were taken. Direct switcher subjects were instructed to continue their current pack of tablets until starting on study drug.

4.5.2 Admission period

After results of routine laboratory tests and Pap smear were received and a subject qualified for participation, she was seen for the Admission Visit. Interval history and vital signs were performed. Diaries and 1 compact of CTR 99, CTR 77 or Ortho-Novum 7/7/7 were dispensed at the Admission Visit, diaries and two compacts at Cycle 1 visit, and diaries and three compacts at Cycle 3 visit, each compact containing 28 tablets. Each subject performed a home urine pregnancy test immediately before taking the first tablet of the first compact. Starters were to start study drug on the first Sunday following the first day of her first menstruation after Admission Visit. Switchers were also told to follow a Sunday start regimen regardless of whether they were Sunday starters on their current pill.

4.5.3 Treatment period

Subjects were seen for Cycle 1, 3, and 6 (or End of Study) Visits between Days 15-21 of the cycle. At each of these visits, vital signs, weight, and interim history were performed, the daily diaries and cycle compacts were reviewed and collected, and AE and concomitant therapies were reported. A complete physical exam, Pap smear, routine laboratory tests, urinalysis, and serum pregnancy test were repeated only at Cycle 6 (or at End of Study) Visit. Each subject was contacted by telephone approximately one month after their completion of participation in the study for a Post-Treatment Evaluation. At this evaluation, post-treatment medications, evaluations, and AEs were reported. If a subject was not reached by telephone, she was contacted by mail.

A pregnancy test was also done whenever pregnancy was suspected during the study period. Pregnancy testing was prompted by failure of withdrawal bleeding. Testing was not done at each visit. All pregnancies reported during the study and post-treatment period were followed for pregnancy outcome and a pregnancy follow-up form completed.

4.6 Evaluation criteria (methods)

4.6.1 Contraceptive Efficacy

The sponsor classified pregnancies into three categories: pretreatment, in-treatment, or post-treatment. Pretreatment pregnancies were those in which conception occurred prior to intake of study drug. In-treatment pregnancies were those in which conception occurred after the first tablet was taken and prior to discontinuation of the study drug. Post-treatment pregnancies were those in which conception occurred after discontinuation of the study drug. Pregnancy tests were not done at every visit. Pregnancy tests were performed only at Screen Visit, at home immediately before taking the first tablet for the first cycle, at Cycle 6 Visit (between Days 15-21 of the cycle), or at End of Study. If pregnancy was suspected during the study period, then pregnancy testing was performed. It is unclear from the Study Schedule if a pregnancy test was performed at the one month Post-treatment telephone call.

> **Reviewer's comment: many contraceptive trials include subjects who become pregnant within 7-14 days of the last study dose as "in-treatment" pregnancies. This issue is discussed later in this review in the Section titled Pregnancies conceived POST discontinuation of study drug.**

The date of conception was determined by using the following information in descending order of accuracy:

1. ultrasound,
2. quantitative serum β-hCG determination,
3. qualitative urine β-hCG determination,
4. estimation of gestations age based on pelvic and/or abdominal examination or pregnancy outcome,
5. daily diary information (e.g. absence of withdrawal bleeding, subjects complaints), or
6. investigator estimation in the absence of the above criteria for the determination of the conception date.