The Independent
MEDICINES & MEDICAL DEVICES
Safety Review

The Independent Medicines and Medical Devices Safety Review

Written Evidence

Manufacturers of Hormone Pregnancy Tests

Published December 2018

Contents

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WARNING: Please be aware some evidence contains descriptions, pictures and audio of the harm suffered by individuals. Some may find this distressing.

Ms. Valerie Brasse
Review Secretary
The Independent Medicines & Medical Devices Safety Review
Room 3.25b
Shepherd's House
King's College
London SE1 1UL

Dear Ms Brasse

The Independent Medicines & Medical Devices Safety Review –
Re: Primodos

////////////////
13th December 2018

Mark Wilkinson
Head of Legal and Compliance
Bayer plc
400 South Oak Way
Green Park
Reading
Berkshire RG2 6AD
United Kingdom

email: [redacted]

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in England No. 935048

Registered office:
Bayer plc
400 South Oak Way
Reading
Berkshire RG2 6AD

We refer to our previous communications concerning the draft Terms of Reference for this review, and the request that we answer certain questions on that aspect of the review which concerns hormone pregnancy tests, set out in the Review Team's email of 16 November 2018. Our answers are enclosed, together with certain historical documents you were seeking. We hope you find this helpful.

We should emphasize that dealing with these questions for any company would be very difficult, given that they largely address events relating to the marketing of a product over 40 years ago. In our case the difficulty is accentuated as Bayer companies never marketed Primodos and their involvement only arises through the acquisition of Schering in 2006. We, therefore, have no first-hand knowledge of the history of the matter and the actions of Schering. The documents on this product held by Schering Chemicals in their old premises were long since destroyed. If the key scientific and medical staff involved in the relevant period at either Schering Chemicals or its parent company are still alive (which we doubt) they are certainly not employees of Bayer plc today.

We are able to provide fairly detailed answers to some of your questions because the UK lawyers for Schering Chemicals at the time of the litigation maintained in their archives a selection of key regulatory documents relating to the history of marketing in the UK. It is these documents that have been used to answer your questions and we should, therefore, note that Bayer plc is not in a position to confirm the completeness or accuracy of the information provided, although we believe that it is likely to be accurate given the historical documents that we have been able to provide.

Against this background and given there is nobody at Bayer plc who could usefully contribute anything on the subject matter of your inquiry, we respectfully decline your offer to attend the oral hearing planned for next year.

Yours sincerely,

Mark Wilkinson

Mark Wilkinson
Head of Legal and Compliance
Bayer plc

Enc

RESPONSE OF BAYER PLC TO THE QUESTIONS OF THE INDEPENDENT MEDICINES & MEDICAL DEVICES SAFETY REVIEW

1. **After the effective date, 1st September 1971, of the Medicines Act 1968, products already on the market were granted a Product Licence of Right. For what time period did the Product Licence or Right apply to Primodos? Was the pregnancy test indication included on the Product Licence of Right application, if so please provide details.**

   Primodos and other similar products were granted Product Licences of Right ("PLR") when the provisions of the Medicines Act 1968 became effective. The PLR for Primodos was sought and approved in late 1971. By that time, Schering Chemicals Ltd (as the UK affiliate was then known) had ceased in 1970 to recommend use of Primodos as a Hormone Pregnancy Test ("HPT") and, therefore, the approved indication was "secondary amenorrhoea" with the Package Leaflet explaining "Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration not due to pregnancy, by the production of a withdrawal bleeding". The PLR was renewed without amendment being sought by the Medicines Division of the Department of Health (as the regulatory authority was then called) in September 1977. Copies are attached (**Attachment 1**). The product was discontinued in 1978 on commercial grounds and, therefore, no further renewal took place.

   The change in indication in 1970 to cease recommending use of Primodos as a HPT was prompted by the intervention of the Standing Joint Committee on the Classification of Proprietary Preparations (see below at Q6).

2. **Was an application for marketing authorisation made after 1 September 1971? If so, please supply details including details of clinical data.**

   No new application for authorisation was sought at any time after September 1971. An application was made for renewal in 1977 which was granted. This application did not require the submission of pre-clinical or clinical data.

3. **Hormonal pregnancy tests were not reimbursed via the usual mechanisms. Please can you provide details of reimbursement arrangements for use of Primodos.**

   As a medicinal product with a marketing authorisation that was for supply on a prescription only basis, doctors were entitled to prescribe the product on a NHS prescription form (or indeed on a private prescription not funded by the NHS). In all such cases, we understand that prevailing NHS rules required specific information to be included on the form, but this did not then (and does not now) include the purpose for which the doctor was prescribing the product. Subject to prevailing statutory prescription changes and exceptions, we are not aware of any reason why the cost of a prescription would not be fully reimbursed and no payment to the dispensing pharmacist by the patient would be required.

4. **Please could you provide a timeline outlining your understanding and recognition of perceived risks associated with the use of hormonal pregnancy tests. This may**

include: initial recognition of the perceived risk, dates of consequential and significant research studies, and communication of regulatory and professional guidance to clinicians and patients.

We understand that your question is referring to the former product Primodos. Please understand that Bayer took over Schering in 2006 which was over 20 years after Primodos ceased to be marketed in the UK. No key medical or scientific staff who were involved with risk assessment within Schering Chemicals or its parent company Schering AG in the 1960s-1970s who could provide such information are still employees of Bayer.

Bayer are aware, however, that at no time did Schering AG consider that the available pre-clinical, clinical and epidemiological evidence established a well-founded suspicion that use of Primodos in pregnancy increased the incidence of congenital malformations in the new-born. The conclusions of Schering and their scientists are entirely consistent with the view of independent expert bodies that have looked at all the available evidence, including the ad hoc Expert Group convened by UK ministers under the auspices of the CHM that considered all scientific evidence available today and concluded, in late 2017, that the available evidence does not support the existence of a causal relationship between use of Primodos and adverse outcomes to pregnancy.

5. **Please can you provide dates of product availability as a pregnancy test, in the UK, Europe and worldwide. Please provide dates for which Primodos was marketed and promoted as a pregnancy test.**

   In different presentations, Primodos was marketed in the UK as a HPT from 1958 to 1970. By 1970 active promotion of Primodos had ceased in the UK. It was, thereafter, available for secondary amenorrhoea not due to pregnancy from 1970 to 1978 when it was voluntarily discontinued for commercial reasons. For the reasons explained before, it is difficult to provide a complete picture of the marketing of Primodos by the Schering Group in the rest of the world. Bayer is aware of, however, (and has already commented upon) a letter from Schering AG, obtained by a Member of the Association on a date unknown, that indicates that Schering AG asked its worldwide affiliates in January 1974 to amend the recommendations for use of Primodos (or the equivalent product) so that Primodos was no longer recommended for use as a pregnancy test. However, by that time some regulatory authorities had already sought changes in such recommendations for either or both of oral and injectable HPTs and, as we have explained, Schering Chemicals in the UK had already made that change at the request of the McGregor Committee in 1970.

6. **In February 1970, the Standing Joint Committee on the Classification of Proprietary Preparations (the McGregor committee) wrote to manufacturers suggesting a deletion of the pregnancy testing indication for hormonal preparations previously recommended for this use. Please provide details of any documents generated in response to this. Please provide details of when the indication was removed from the data sheet.**

   The McGregor Committee - the Standing Joint Committee on the Classification of Proprietary Preparations - functioned between 1967 and 1970 preparing what was known

as the "Proplist", a booklet sent regularly to prescribers. The function of the Committee was to recommend to doctors which preparations should be used in treatment and to identify those preparations the prescribing of which called for special justification. Its primary interest was in efficacy compared with other available interventions. In 1970, the McGregor Committee wrote to all manufacturers, including Schering Chemicals, suggesting the deletion of the indication pregnancy testing from the hormone preparations previously recommended for this use.

In 1970, the functions of the Committee were taken over by the Medicines Commission (formed under the Medicines Act 1968 to advise the Ministers of Health etc. of the UK) and the Committee was disbanded. Steps were taken in 1970, after agreement with the McGregor Committee was reached, to change the product information. The packing leaflet was changed in February 1970 as were information cards (data sheets). New cards became available no later than November 1971 that omitted the reference to pregnancy testing previously included. The available correspondence requested is attached (**Attachment 2**).

7. **Please indicate the exact date when Primodos use was contraindicated in pregnancy. Please detail any correspondence between yourselves and the editors of MIMS regarding the insertion of a contraindication of pregnancy in the MIMS product entry.**

Following the CSM "Yellow Warning" of June 1975, the product information for Primodos was changed to include a contra-indication for use in pregnancy and a warning reflecting the CSM statement. Use and dissemination of new informational materials was agreed with the UK Licensing Authority.

The new materials included a revised packing slip that was developed and printed by Schering AG in September 1975 and the first new stocks containing it arrived in the UK in August 1976. However, in the interim all existing stock was over-labelled with a sticker containing the CSM warning as follows:

> "**WARNING**
>
> **Not to be taken during pregnancy**
>
> A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities. Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant."

The text of the Data Sheet for Primodos was also changed immediately following the June CSM "Yellow Warning" to indicate a contra-indication of pregnancy and the CSM warning. This required the approval of the Licensing Authority which was given. In 1974, the first Association of British Pharmaceutical Industry Compendium of data sheets was issued. In placing its data sheets in the Compendium (distributed free to doctors) a company ensured compliance with s96 of the Medicines Act 1968. Accordingly, the compendium became the standard method of supplying prescribing information to the doctor. Entries appeared for Primodos each year 1974-78. That for 1975 had already been printed and supplied when the CSM issued their yellow warning in June 1975. The first entry with the addition of a contraindication appeared in the 1976 Edition.

Schering Chemicals also wrote a standard letter to all UK doctors, wholesalers and pharmacists in June 1975 to draw their attention to the CSM warning. Letters were also sent to the relevant trade journals. Promotion of Primodos through advertising had long since ended, but the warning sticker was inserted on all copies of Schering's reference compendium describing all its hormone based products and their uses. A copy of a letter of 18 July 1975 to the Medicines Division at the DHSS, explaining all the steps taken to ensure knowledge of the contra-indication and the warning and the ABPI Data Sheet entry for 1976, is attached. (**Attachment 3**).

MIMS ("Monthly Index of Medical Specialities") was a commercial publication of Haymarket Publishing Ltd., Medical Division, sent free each month to general practitioners, to all heads of hospital pharmacy departments and on rotation to selected hospital doctors and consultants in the UK. It contained brief prescribing information on products being marketed in the UK under generic headings such as "Analgesics" or "Oral Contraceptives". Primodos was listed under "Gonadal hormones and related synthetic compounds." Prior to the introduction of the ABPI Data Sheet Compendium, MIMS also published an annual compendium. Although information is sent to MIMS by the manufacturer, an independent review board of specialists prepares the editorial notes and has ultimate control over the nature of the entries for each preparation.

On 5 June 1975, Schering UK wrote to the publishers of MIMS to have the entry for Primodos in MIMS changed to include the contra-indication of pregnancy. The Editor of MIMS initially said this was unnecessary as the indication for Primodos specifically excluded use in conditions due to pregnancy (or potential pregnancy). Schering pushed back on this assessment and eventually, in July 1975, MIMS agreed to include a statement that the product should only be used for secondary amenorrhoea of short duration "where pregnancy has been excluded". This entry was discussed with the Medicines Division of the Department of Health that agreed to this language which was also made an approved variation to the product authorisation in September 1975. Copies of requested correspondence appear in **Attachment 4**.

8. **Please can you provide dates of product withdrawal, in the UK, Europe and worldwide. Please detail if these were voluntary withdrawals.**

The decision to discontinue the marketing of Primodos in the UK was taken by Schering Chemicals in January 1978 for commercial reasons (**Attachment 5**). The authorisation for Primodos was voluntarily surrendered in 1978. Bayer plc is unable to provide comparable information for Schering's activities in the rest of the world.

9. **Please can you provide details of your relevant policies and protocols from 1950-1980, if any, for ensuring that information relevant to patient safety, and learning from adverse events is disseminated. Please detail how any changes in indication, contraindications and withdrawals were communicated by yourselves to clinicians and patients.**

Bayer plc is unable to provide any information on the historical policies of Schering Chemicals or Schering AG relating to development and communication of such information, save to the extent of the description of action taken in relation to the 1975 contra-indication of pregnancy in the UK described above.

10. **Please can you describe the elements of your corporate social responsibility policy which relate to the availability of products, and the risk-benefit analysis for products that you manufacture?**

The policies of Bayer plc on such matters are irrelevant to the manufacture and marketing of Primodos, as Bayer plc never supplied that product. Bayer plc is unable to comment on the policy on such matters of Schering Chemicals or Schering AG in the years 1958-1978 or at all.

11. **If applicable, please can you provide a brief summary of litigation and/or settlements relevant to your product(s), both within the UK and worldwide?**

Bayer plc never marketed Primodos in the UK, but is aware that a Group action was commenced against Schering Chemicals and Schering AG in 1977 in which plaintiffs alleged that Primodos had caused congenital malformations and Schering had been negligent. The case was funded by legal aid for many years, but was discontinued immediately before a lengthy trial was due to start.

In April 1982, following the exchange of supplementary expert reports, the claimants applied for an adjournment of the trial date in part because the claimants' legal team was obliged to re-evaluate the merits of the case and report to the Legal Aid Board. The trial was adjourned until October 1982, but in July 1982 the claimants applied to Mr Justice Bingham (as he then was) to discontinue the proceedings. We have a transcript of the proceedings and Queen's Counsel for the claimants explained to the Court that the totality of the epidemiological evidence did not afford any real possibility that it could be established that a causal association existed between use of Primodos and congenital malformations. In addition, the data on biochemical mechanisms that might account for such an association were not viewed as supporting the claimants' original case that plausible mechanisms existed. Nor did the claimants' barristers believe that the animal testing data indicated that Primodos was teratogenic at the dosages used in pregnancy tests. In the circumstances the claimants concluded that discontinuation was appropriate because, as the claimants' Leading Counsel stated:

> "... there is no reasonable prospect - indeed, no real prospect - that we can establish as a matter of probability that Primodos causes congenital malformations."

The Court and presumably the Legal Aid Board (but not the defendants) were supplied with a detailed written opinion of more than 120 pages in length that explained this conclusion.

The Court gave permission to claimants to discontinue their claims, but only on the basis that no further action should be brought in respect of the complaints that were the subject matter of the actions without the leave of the Court and on such terms as the Court might then impose. The Court allowed discontinuation rather than dismissal in case "a scientific revolution or a marked change in the circumstances" justified a different view of the case on causation. In giving permission, however, Mr Justice Bingham made it clear that a "very strong case indeed" would have to be made out by the claimants to show that it was just for the matter to be reopened and he noted that the Court would have to be satisfied that no unreasonable prejudice to the defendants would accrue. He stated that he thought it was very unlikely that leave would be given.

We attach for information a full transcript of the proceedings before judgment and of the judgment itself (**Attachment 6**). No proceedings have been pursued in the UK against Schering or Bayer plc in respect of the subject matter of the original proceedings since 1982. Bayer plc is not aware of any such proceedings in the EU resulting in any decision in favour of claimants and understands that no compensation has ever been paid by Schering Group anywhere in the world as a result of claims relating to Primodos.

12. **Do you contribute to an administrative (non-litigative) redress scheme anywhere in the world, such as the Nordic pharmaceutical insurance schemes? If so, where, and what are the terms of the contribution? What is your evaluation of the scheme?**

Bayer plc has no involvement in any such redress schemes.

December 2018

ATTACHMENT 1

PRODUCT LICENCE OF RIGHT No. 0033/5027

LICENSING OFFICE
DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33/37A FINSBURY SQUARE
LONDON, EC2A 1PP

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APPLICATION FOR LICENCE OF RIGHT

TO MARKET

PRIMODOS COATED TABLETS 10 mg.

==========

Schering Chemicals Limited
Burgess Hill
Sussex

PRODUCT LICENCE OF RIGHT No. 0053/5027

1. NAME AND ADDRESS OF THE APPLICANT

Schering Chemicals Limited
Burgess Hill
Sussex

LICENSING OFFICE
DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33/37A FINSBURY SQUARE
LONDON, EC2A 1PP

2. NAME AND ADDRESS OF THE PROPOSED LICENSEE

Schering Chemicals Limited
Burgess Hill
Sussex

3. ROLE OF PROPOSED LICENSEE

The proposed licensee imports the product from Germany for sale in the United Kingdom.

4. NAME AND ADDRESS OF THE ACTUAL IMPORTER

As for 2

5. PERIOD OF VALIDITY OF THE LICENCE

Five years

6. ACTIVITIES COVERED BY THE LICENCE

The licence will authorise the importation of the product and its sale and supply in the United Kingdom.

PRODUCT LICENCE OF RIGHT No. 0053/5027.

LICENSING OFFICE
DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33/37A FINSBURY SQUARE
LONDON, EC2A 1PP

7. Name of Medicinal Product:

Primodos

8. Pharmaceutical Form:

Tablet for oral administration to human beings

9. Composition:

(a) Active ingredients

1 coated tablet contains:

10.0	mg.	Norethisterone acetate
0.02	mg.	17α-ethinyl oestradiol

(b) Other ingredients

1 coated tablet contains:

1.00	mg.	Magnesium stearate
44.98	mg.	Starch
69.00	mg.	Lactose
50.615	mg.	Sugar
29.628	mg.	Talc
2.999	mg.	Calcium carbonate, precipitated
0.56	mg.	Polyvinylpyrrolidone K90 (Luviskol K90)
0.078	mg.	Gelatin
0.005	mg.	Sodium benzoate
0.08	mg.	White wax
0.04	mg.	Carnauba wax
0.995	mg.	Tartrazine, food colour yellow No. 2.

PRODUCT LICENCE OF RIGHT No. 0033/5027

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LONDON, EC2A 1PP

10. Physical Characteristics:

Orange-yellow, lustrous coated tablets of about 7.8 mm diameter and about 4.3 mm height

11. Clinical Use:

(a) Recommended clinical use

Secondary Amenorrhoea

(b) Route of Administration

Oral

(c) Recommended dosage

Adults

1 tablet on each of two consecutive days. Bleeding usually follows in 3 - 6 days.

Children

Not for administration to children

12. Standard Provisions:

No comment

PRODUCT LICENCE OF RIGHT No. 0053/5027

SCHERING AG

Pharma Koordination

23.2.1971

13. Manufacture and Assembly

(a) Summary of manufacturing procedure

Abridged Manufacturing Formula

Primodos

1. Granulation

1.1 Starch paste

1.1.1 A portion of the starch is stirred into the demineralized water.

1.1.2 Levigation (1.1.1) is added to boiling, demineralized water and heated till it forms a paste.

1.2 Manufacturing of granulation

1.2.1 Ethinyl estradiol is dissolved in alcohol.

1.2.2 Solution (1.2.1) is mixed with some of the starch.

1.2.3 Mixture (1.2.2) is dried.

1.2.4 Norethisterone acetate micro 2 is mixed with some of the lactose.

1.2.5 Mixture (1.2.3) is screened and mixed with preparation (1.2.4), with lactose and with a portion of the starch.

1.2.6 The powder mixture (1.2.5) is kneaded with the starch paste (1.1).

1.2.7 The moist mass (1.2.6) is granulated and dried.

1.2.8 The dried granules are made uniform.

1.2.9 The uniform granules (1.2.8) are mixed with magnesium stearate and the remainder of the starch.

2. Cores

The granulation is pressed to form cores.

3. Coated tablets

3.1 Preparations for applying the tablet coating.

SCHERING AG

13. (a) 3.1.1 Suspension

3.1.1.1 Polyvinylpyrrolidone K 90 is dissolved in benzene-denatured alcohol.

3.1.1.2 A portion of the talc is suspended in the solution (3.1.1.1)

3.1.2 Solution I

3.1.2.1 Gelatin and sodium benzoate are dissolved in demineralized water.

3.1.2.2 A portion of the sucrose is dissolved in demineralized water.

3.1.2.3 Solutions (3.1.2.1) and (3.1.2.2) are mixed.

3.1.3 Solution 2

Identical to solution (3.1.2.2)

3.1.4 Color solution I

A portion of the food-color yellow No. 2 and a portion of the sucrose are dissolved in demineralized water.

3.1.5 Color solution 2

The remainder of the food-color yellow No. 2 and the remainder of the sucrose are dissolved in demineralized water.

3.1.6 Powder

The precipitated calcium carbonate is mixed with the talc.

3.1.7 Wax mixture.

3.1.7.1 White wax and carnauba wax are melted together.

3.1.7.2 The inside of the pan is coated with the melt (3.1.7.1).

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SCHERING AG

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DEPARTMENT OF HEALTH AND SOCIAL SECURITY
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33/39 FINSBURY SQUARE
LONDON, EC2A 1PP

13 (a) 3.2 Coating

3.2.1 Suspension (3.1.1) is applied to the cores.

3.2.2 Solution I (3.1.2) and the powder (3.1.6) are applied.

3.2.3 Solution 2 (3.1.3) is applied.

3.2.4 Color solution I (3.1.4) is applied.

3.2.5 Color solution 2 (3.1.5) is applied.

3.3 Polishing

The coated tablets are polished in the wax pan (3.1.7.2). They are finally dried.

(signed by Dr. Busse)

PRODUCT LICENCE OF RIGHT No. 0053/5027.

13. (b) Manufacture and assembly of this preparation take place at the production plants of Schering AG., Berlin/Bergkamen at the following addresses:

1 Berlin 65
Müllerstrasse 170-172
Germany

LICENSING OFFICE
DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33/37A FINSBURY SQUARE
LONDON, EC2A 1PP

(c) Manufacturer

Schering AG., Berlin/Bergkamen,
Berlin 65
Mullerstrasse 170-172
Germany

(d) Storage

Pending Customs clearance at Shoreham Port the imported products are stored at the following address:

P.D. Wharfage Co. Ltd.,
Aldrington Basin
Shoreham, Sussex

After a period of temporary storage the goods are transferred to one of the following addresses:

Schering Chemicals Limited
(Warehouse)
Victoria Way
Burgess Hill
Sussex

or

(Warehouse)
London Road
Burgess Hill
Sussex

Conditions of even temperature and humidity exist in all premises and comply with the manufacturers' specifications for storage of the product.

PRODUCT LICENCE OF RIGHT No. 0033/5027

14. Quality control over method of pharmaceutical manufacture:

(a) Tablet and coated tablet preparations

Control measures during manufacture

1. Active and inactive substances are employed for manufacturing processes in the production unit only after being released by the analytical control laboratory.

2. Granulations are prepared according to a batch production sheet which has been prepared by the unit director or a person whom he has designated. The initial weights of active and inactive substances are always determined by two persons, the unit director and/or persons designated by him. Both persons must sign the batch production sheet.

3. A sample of the finished granulation is sent to the analytical control laboratory for testing according to the testing standard currently in effect.

4. Following release, the granulation is compressed to form tablets or tablet cores. In the course of this process, the weight, height, hardness and disintegration speed of the unfinished pressings are tested at regular intervals and the results entered on the work record sheets.

5. Samples of the finished tablets or cores are turned over to the analytical control laboratory for testing according to the appropriate testing standard.

6. Following release by the analytical control laboratory, the cores are weighed on a regular basis during the coating process in accordance with the specifications contained in the manufacturing formulas.

7. The coated tablets are tested in the analytical control laboratory according to the testing standard 2 D 01 07 c.

8. After the lots of tablets and coated tablets have been released, the unit director or his authorized representative checks identity (form, size, color, weight) against the specifications on the lot cards before packaging begins.

9. Reserve specimens from each lot are retained for some years both in the analytical control laboratory and at the manufacturing unit.

PRODUCT LICENCE OF RIGHT No. 0053/5027

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LONDON, EC2A 1PP

14. (b) Our Parent Company, Schering AG., Berlin/Bergkamen, as manufacturer of the product, is responsible for deciding whether any batch is of acceptable quality for marketing

15. Containers:

Primodos is supplied in a two-tablet foil pack

16. Labelling:

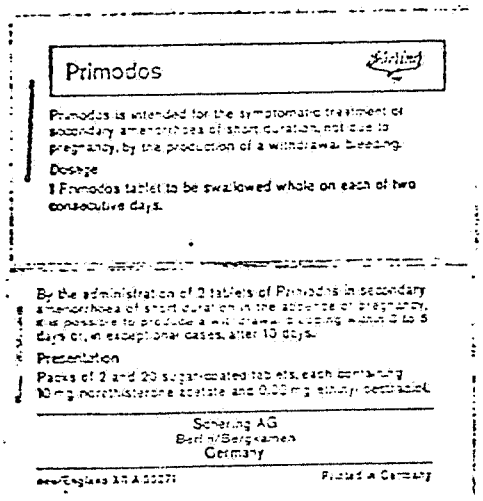
(a) Container

Oral

(b) Package

No special directions

(c) Package Leaflet



Primodos

Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy, by the production of a withdrawal bleeding.

Dosage
1 Primodos tablet to be swallowed whole on each of two consecutive days.

By the administration of 2 tablets of Primodos in secondary amenorrhoea of short duration in the absence of pregnancy, it is possible to provoke a withdrawal bleeding within 2 to 5 days or, in exceptional cases, after 10 days.

Presentation
Packs of 2 and 20 sugar-coated tablets, each containing 10 mg norethisterone acetate and 0.050 mg ethinyl oestradiol.

Schering AG
Berlin/Bergkamen
Germany

Printed in Germany

PRODUCT LICENCE OF RIGHT No. 0053/5027

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FINSBURY SQUARE HOUSE
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LONDON, EC2A 1PP

17. Method of Sale and Supply:

(a) This preparation was made available, on prescription only, prior to 1964.

(b) Entry from MIMS Monthly Index, August, 1971.

PRIMODOS Schering
Norethisterone acetate 10 mg., ethinyloestradiol 0·02 mg.; tab.
Amenorrhoea not due to pregnancy.
2, 29p.; also 20.
1 on two consecutive days.

(c) No changes in the method of sale and supply of this product are proposed

18. Therapeutic Substances Act and Diseases of Animals Act:

Not applicable

MEDICINES ACT 1968 AND 1971

FIRST RENEWAL OF PRODUCT LICENCES OF RIGHT

The Product Licence(s) of Right described on page 2 and continuation sheet(s) No(s): / of the attached renewal application are hereby renewed, subject to the conditions set out or referred to on page 1 of the said application. 65

Renewed licence(s) described in Part 1 of the attached Schedule shall be subject to further provisions set out or referred to in Part 2 of the said Schedule

The licence(s), as renewed, will, unless previously suspended, revoked or varied as to their validity, continue in force until 31 AUG 1980

DEPARTMENT OF HEALTH AND SOCIAL SECURITY

Signature:

Date renewed: 27 September 1977

Department of Health and Social Security
Medicines Division
Finsbury Square House
33-37a Finsbury Square
London EC2 1PP

AUTHENTICATION - For the purpose of authentication this document and all the pages of the attached application will bear the signature of the Certifying Officer and the authorisation stamp of the Department of Health and Social Security, Medicines Division.

NOTICE

1. The existence of a product licence of right in respect of a particular product does not mean that the safety, quality or efficacy of the product has been considered by the licensing authority.

2. The licensing authority is currently engaged in the review of products in respect of which licences have been granted. For this purpose the licensing authority receives advice on the safety, quality and efficacy of the said products from the Committee on Review of Medicines established under the provisions of The Medicines (Committee on the Review of Medicines) Order 1975 (SI 1975 No 1006). The licensing authority may act upon the advice of the Committee on the Review of Medicines for the purpose of the procedure provided in Schedule 2 to the Medicines Act 1968 in relation to revocation, suspension or variation of any product licence in connection with the above-mentioned review.

3. After a date to be fixed by statutory order under Section 52 of the Medicines Act 1968, it will not be lawful (notwithstanding any provision in the relevant licence of right) to sell by retail any medicinal product otherwise than from a registered pharmacy unless the product is included on a general sale list or is covered by one of the statutory exemptions under sections 55 or 56 of the Act or by any exemption made by order under section 57 of the Act.

APPLICATION FORM FOR THE RENEWAL OF PRODUCT LICENCES OF RIGHT

Approved by the Licensing Authority under Regulation 2(2) of SI 1974 No 832 for first renewals of product licences of right where:

i. the licence holders reference number ends with a figure 50 - 74

ii. the licence holder desires the licence to be renewed until 31 August 1980 subject to the conditions set out in this form

FULL NAME AND ADDRESS OF LICENCE HOLDER:	SCHERING CHEMICALS LIMITED PHARMACEUTICAL DIVISION, THE BROW, BURGESS HILL, SUSSEX, RH15 9NE.
LICENCE HOLDER'S CODE NUMBER	0053
NUMBER OF CONTINUATION SHEETS (IF ANY)	ONE

1. Application is hereby made for the renewal of the product licences described overleaf and on the continuation sheets until 31 August 1980 subject to the conditions mentioned in paragraph 4 below.

2. I confirm that apart from variations approved by and changes notified to the Licensing Authority up to this date no material change has taken place in respect of any of the matters included in the original application.

3. The particulars mentioned in paragraph 5 of the Schedule I to SI 1974 No 832 are omitted from this application form as the information

   a. was given in the original application or

   ✓ b. has been or will be given in connection with requests for information made in connection with the review of product licences.

4. The renewed licences shall be subject to the following conditions:

   a. all the conditions of the original licence

   b. all the standard provisions applicable to products of the same description under regulations under Section 47 which are in force at the date the licences are renewed.

PARTICULARS

LICENCE NUMBER	NAME OF PRODUCT
0053/5000	GYNOVLAR 21
0053/5001	SCEERIPROCT SUPPOSITORIES
0053/5002	SCHERIPROCT OINTMENT
0053/5003	ULTRALANUM OINTMENT .
0053/5004	GONDAFON
0053/5005	ULTRALANUM OINTMENT PLAIN
0053/5006	UROGRAFIN 325 (58%)
0053/5007	UROGRAFIN 150 (30%) FOR INFUSION
0053/5008	ULTRAPROCT OINTMENT
0053/5009	ULTRAPROCT SUPPOSITORIES
0053/5010	MINOVLAR
0053/5011	ULTRALANUM CREAM PLAIN
0053/5012	SH 420
0053/5014	CONTROVLAR
0053/5015	ULTRADIL OINTMENT PLAIN
0053/5016	MINOVLAR ED
0053/5017	ULTRADIL CREAM PLAIN
0053/5018	UROGRAFIN 310M (65%)
0053/5019	ANOVLAR
0053/5022	ENDOGRAFIN
0053/5023	GASTROGRAFIN

N O T E

1. All continuation sheets are to be serially numbered
2. Extra continuation sheets should be reproductions of the enclosed copy or of the pattern.
3. Applications should be made in sets containing not more than 20 sheets each.

SIGNATURE [signature] DATE 19th April, 1977.

STATUS HEAD OF MEDICAL SCIENTIFIC CO-ORDINATION.

F O R O F F I C I A L U S E

RENEWAL OF THE LICENCES DESCRIBED ABOVE IS HEREBY AUTHORISED

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33-37A FINSBURY SQUARE, LONDON, EC2A 1PP

SIGNED [signature]

DATE 27/4/77

P A R T I C U L A R S

Continuation Sheet No. 1

LICENCE NUMBER	NAME OF PRODUCT
0053/5027	PRIMODOS
0053/5031	PRIMOLUT DEPOT 250 mg.
0053/5032	PRIMOLUT DEPOT 500 mg.
0053/5033	PRIMOLUT N
0053/5037	PRIMOTESTON DEPOT 250 mg.
0053/5038	SCHERICUR
0053/5039	DEPOSTAT (for endometrial cancer)
0053/5040	PRIMOBOLAN TABLETS 5 mg.
0053/5041	UROGRAFIN 150 (30%)
0053/5042	UROGRAFIN 45%
0053/5043	UROGRAFIN 290 (60%)
0053/5044	UROGRAFIN 370 (76%)
0053/5048	BILOPTIN
0053/5049	SOLU-BILOPTIN
0053/5050	BILOPTIN FATTY MEAL

SIGNATURE.. DATE 19th April, 1977.

F O R O F F I C I A L U S E

RENEWAL OF THE LICENCES DESCRIBED ABOVE IS HEREBY AUTHORISED

SIGNED.....

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FINSBURY SQUARE HOUSE
33-37A FINSBURY SQUARE, LONDON, EC2A 1PP

DATE 27/9/77

MEDICINES ACT 1968 AND 1971

FIRST RENEWAL OF PRODUCT LICENCES OF RIGHT

SCHEDULE

Part 1 - Particulars of licences subject to further provisions

LICENCE NUMBER(S):

0053/5000	5011	5031	5047
5001	5012	5032	5050
5002	5014	5033	
5003	5015	5037	
5004	5016	5038	
5005	5017	5039	
5006	5018	5041	
5007	5019	5042	
5008	5022	5043	
5009	5023	5044	
5010	5027	5048	

Part 2 - Further provisions which shall apply to the licences specified in Part 1

1. The manufacturer shall provide and maintain such staff, premises, and plant as are necessary for the carrying out in accordance with the relevant product licences of such stages of the manufacture and assembly of the medicinal products to which the relevant product licences relate as are undertaken by him.

2. The manufacturer shall provide and maintain such staff, premises, equipment and facilities for the handling, storage and distribution of the medicinal products to which the relevant product licences relate which he handles, stores or distributes as are necessary to avoid deterioration of the medicinal products.

3. The manufacturer shall conduct all manufacture and assembly operations in such a way as to ensure that the medicinal products to which the relevant product licences relate conform with the standards of strength, quality and purity applicable to them under the relevant product licences.

4. Where animals are used in the production of any medicinal product and the relevant product licences contain provisions relating to them the manufacturer shall arrange for the animals to be housed in premises of such a nature and to be managed in such a way as will facilitate compliance with such provisions.

5. The manufacturer shall make such adequate and suitable arrangements as are necessary for carrying out in accordance with the relevant product licences any tests of the strength, quality or purity of the medicinal products to which the licences relate.

6. The manufacturer shall inform the holder of the relevant product licences of any material alteration in the premises or plant used in connection with the manufacture or assembly of the medicinal products to which the relevant product licences relate or in the operations for which such premises or plant are so used and of any change, since the granting of the relevant product licences in respect of any person -

(a) responsible for supervising the production operations, or

(b) responsible for quality control of the medicinal products to which the relevant product licences relate, or

(c) in charge of the animals from which are derived any substance used in the production of the medicinal products to which the relevant product licences relate or

(d) responsible for the culture of any living tissues used in the manufacture of the medicinal products to which the relevant product licences relate.

7. The manufacturer shall keep readily available for inspection by a person authorised by the licensing authority durable records of the details of manufacture and assembly of each batch of every medicinal product to which each relevant product licence relates and of the tests carried out thereon in such a form that the records will be easily identifiable from the number of the batch as shown on each container in which the medicinal product is exported from the country where it has been manufactured or assembled; the manufacturer shall permit the person authorised to take copies of or make extracts from such records. Such records shall not be destroyed for a period of five years from the date when the manufacture or assembly of the relevant batch of the medicinal product occurred.

8. The manufacturer shall inform the holder of the relevant product licence of any material change since the date upon which such licence was granted in respect of -

(a) the facilities and equipment available at each of the premises of the manufacturer for carrying out any stage of the manufacture or assembly of the medicinal products to which the relevant product licences relate, or

(b) the facilities and equipment available in each of the premises of the manufacturer for the storage of the medicinal products to which the relevant product licences relate on, and distribution of the products from or between, such premises, or

(c) any manufacturing operations, not being operations in relation to the medicinal products to which the relevant product licences relate, which are carried on by the manufacturer on or near any of the premises on which such medicinal products are manufactured or assembled and the substances or articles in respect of which such operations are carried on, or

(d) the arrangements for the identification and storage of materials and ingredients before and during manufacture of the medicinal products to which the relevant product licences relate and the arrangements for the storage of the medicinal products after they have been manufactured or assembled, or

(e) the arrangements for ensuring a satisfactory turnover of stocks of medicinal products to which the relevant product licences relate, or

(f) the arrangements for maintaining production records and records of analytical and other testing procedures applied in the course of manufacture or assembly of the medicinal products to which the relevant product licences relate, or

(g) the arrangements for keeping reference samples of materials used in the manufacture of any medicinal products to which the relevant product licences relate and reference samples of such medicinal products.

ATTACHMENT 2

STANDING JOINT COMMITTEE ON THE CLASSIFICATION
OF PROPRIETARY PREPARATIONS
Queen Anne's Mansions, Queen Anne's Gate, LONDON S.W.1
Telephone: 01-839 9020, *ext.* 1316

17th February, 1970

The Medical Director
Schering Chemicals Limited
Victoria Way
Burgess Hill
Sussex

Dear Sir,

PRIMODOS

The Committee has decided to classify a number of products on the basis of published information without putting the manufacturer to the trouble of providing clinical evidence.

The Committee would be prepared to place the product in A.3 if the promotional indication as a "pregnancy test" were withdrawn, and I would suggest that the most appropriate and, acceptable to the Committee, promotion be " symptomatic treatment of amenorrhoea to produce withdrawal bleeding".

This matter has also been taken up with other manufacturers.

For Primodos we took the formula Norethisteron acetate 10 mg and Ethinyloestradiol 0.02 mg./ 1 tablet to be taken on two consective days and we shall be glad if you would confirm that these details are correct.

I shall be grateful for an early reply in order that we may proceed with the appropriate entry in Proplist.

If you do not wish to have the product placed in this category for the indications suggested, you should give the Secretary notice of appeal within fourteen days and the appeal should then be submitted with relevant evidence in two months.

Yours faithfully

S. Ruttle

S RUTTLE MD MRCP(Ed) DCH
Medical Assessor

S. Ruttle, Esq., M.D., M.R.C.P.(Ed), D.C.H.,
Medical Assessor,
Standing Joint Committee on the Classification
of Proprietary Preparations,
Queen Anne's Mansions,
Queen Anne's Gate,
LONDON S.W.1.

MS/JC

9th March, 1970.

Dear Dr. Ruttle,

With reference to your letter of the 17th February regarding the classification of PRIMODOS, we agree to the deletion of "pregnancy test" from the indications, and to the promotional statement "the symptomatic treatment of amenorrhoea not due to pregnancy, by producing withdrawal bleeding".

The details of the constituents and the dosage are correct.

Yours sincerely,

Maxine Staniford, M.B., Ch.B., D.P.H.,
Head of Medical Information.

IG 11

STANDING JOINT COMMITTEE ON THE CLASSIFICATION
OF PROPRIETARY PREPARATIONS
Queen Anne's Mansions, Queen Anne's Gate
LONDON S.W.1
Telephone: ~~trafalgar~~ 9020, *ext.* 1304
01-839

Your Ref: MS/JC
Our Ref: B/C26/SCH-1/12

Dr M Staniford MB ChB DPH
Head of Medical Information
Schering Chemicals Ltd
Pharmaceuticals Division
Victoria Way
Burgess Hill
Sussex

8 April 1970

Dear Dr Staniford

Thank you for your letter of 9 March addressed to Dr Ruttle.

Accordingly the Committee have agreed that Primodos should be classified A3.

Yours faithfully

A B Rees
Secretary

1971

Primodos

secondary amenorrhoea

Chemistry

Each tablet contains 10 mg norethisterone acetate BP
0·02 mg ethinyloestradiol BP

Description and mode of action

Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy, by the production of a withdrawal bleeding within 3 to 6 days of tablet taking or, in exceptional cases, after up to 10 days.

Indication

Secondary amenorrhoea of short duration.

Dosage

1 tablet to be taken on each of two consecutive days.

Side-effects

Rarely, a feeling of nausea may occur.

Special precautions

In the rare case in which bleeding does not follow the administration of Primodos (usually when the amenorrhoea has lasted 6 months or longer), although the patient is not pregnant, a careful search for organic disease should be made before giving further hormonal treatment, which should be as for primary amenorrhoea.

Primodos

Presentation and Basic NHS Price

Schedule: P1 S4B

Recognition: Orange sugar-coated tablet, unscored, of 8mm diameter.

Storage: Cool, dry conditions, shelf-life 5 years.

Foil strip of 2 tablets: £0·29
20 tablets: £2·45

Further information is available on request from the Medical Department of Schering Chemicals Limited.

100 YEARS SCHERING
100 YEARS OF PROGRESS

Printed in the UK

Schering Chemicals Limited
Pharmaceutical Division
Burgess Hill, Sussex

Schering AG Berlin/Bergkamen

Reprinted November 1971 PDS2

ATTACHMENT 3

SCHERING
CHEMICALS LIMITED

Pharmaceutical Division

The Brow Burgess Hill. West Sussex RH15 9NE
Telephone Burgess Hill 6011 (STD 044 46)
Cables Scherichem Burgess Hill
Telex 87577

30

Department of Health & Social Security,
Medicines Division,
Finsbury Square House,
33-37A Finsbury Square,
LONDON, EC2A 1PP.

Attn: Miss Weedon.

18th July, 1975.

Your ref

Our ref HMB/LR

Dear Sirs,

Adverse Reaction Warning on Hormonal Pregnancy Tests.

After the issue by the CSM Adverse Reaction Committee of the warning on hormonal pregnancy tests, we took the following action regarding our preparation Primodos.

1. A letter explaining the situation was sent to all G.P's., gynaecologists and family planning doctors (see appendix 1.).

2. A similar letter of explanation was sent to the editors of Chemist & Druggist, Retail Chemist and Pharmaceutical Journal (appendix 2).

3. An adhesive label bearing the warning was produced (appendix 3) and has been attached to all stocks of Primodos held in our warehouse.

4. Stickers were offered to wholesale and retail chemists by our letter sent to wholesalers (appendix 4) and announcements in the trade press.

5. The warning labels were attached to copies of our publication "Synopsis of Hormone Therapy" held in the warehouse and supplies of the labels were sent to our representatives for insertion into copies of the Synopsis in their possession. (appendex 5).

6. A revised data sheet has been prepared (draft copy attached, appendix 6) and should be printed in the near future.

7. A text has been prepared for a new packing insert (appendix 7). This will be printed in Berlin for all future U.K. packs of Primodos.

8. We have contacted Haymarket Publishing Ltd., asking for the words "Contraindication: pregnancy" to be added to the entry for Primodos in MIMS.

We hope this is the information you require.

Yours faithfully,

Heather M. Barker B.Sc.,
Head of Medical Services.

Appendix 1.

SCHERING
CHEMICALS LIMITED

Dear Doctor,

Several years ago Schering Chemicals accepted the argument that the immunological pregnancy-tests were to be preferred to hormone pregnancy-tests, not only on the grounds of the efficacy and speed of the former, but also because of the theoretical argument against the unnecessary administration of any pharmacological agent. The use of our product Primodos as a pregnancy test has not been recommended since that decision. Retrospective epidemiological studies have led to a suspicion that hormonal products such as Primodos might increase the risk of foetal abnormalities if administered in early pregnancy, and although it remains unproved, the Committee on Safety of Medicines has concluded that the suspicion has become strong enough to justify the issuing of an official warning against the misuse of Primodos and related products during pregnancy.

The purpose of this letter is to remind you that Primodos must not be administered unless pregnancy has been excluded and to inform you that the appropriate modifications will be made at once to our literature so as to make even more conspicuous than formerly the fact that pregnancy is a contra-indication.

Yours faithfully,

Schering Chemicals Limited

Appendix 2.

cc: AGP
SJW
BK
JA
WE

DB Same letter sent to -
Retail Chemist and
The Pharmaceutical Journal.

The Editor,
Chemist & Druggist,
25, New Street Square,
London,
EC4A 3JA.

PB/RAB
5th June, 1975.

Dear Sir,

The issue of a new yellow adverse-reactions report by the Committee on Safety of Medicines necessitates urgent action on our part, and we should be most grateful if you would agree to insert in the next copy of your journal the following statement:

Several years ago Schering Chemicals accepted the argument that the immunological pregnancy tests were to be preferred to hormone pregnancy-tests, not only on the grounds of the efficacy and speed of the former, but also because of the theoretical argument against the unnecessary administration of any pharmacological agent. The use of Schering's product Primodos as a pregnancy test has not been recommended since that decision. Retrospective epidemiological studies have led to a suspicion that hormonal products such as Primodos might increase the risk of foetal abnormalities if administered in early pregnancy, and although it remains unproved, the Committee on Safety of Medicines has concluded that the suspicion has become strong enough to justify the issuing of an official warning against the misuse of Primodos and related products during pregnancy.

Schering Chemicals Limited wishes to inform wholesale and retail chemists that adhesive labels carrying the following warning have been printed:

WARNING: NOT TO BE TAKEN DURING PREGNANCY

A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities.
Because of this possible hazard, Primodos must not be taken [illegible] is essential that the patient is not pregnant.

cont./... 2

The Editor,
Chemist & Druggist.

5th June, 1975.

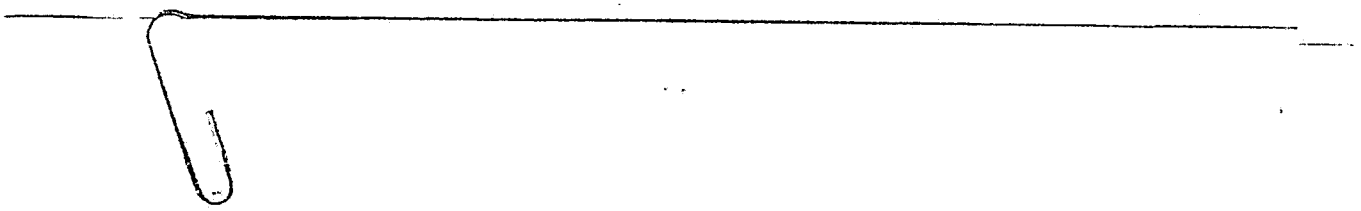
Supplies of these labels in quantities appropriate to stocks held can be obtained from Orders, Schering Chemicals Limited, The Brow, Burgess Hill, West Sussex. Telephone Burgess Hill (STD 0441) 6011 Extension 246.

Yours faithfully,

SCHERING CHEMICALS LIMITED

Appendix 3

Actual size



WARNING

Not to be taken during pregnancy

A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities. Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant.

Appendix 4.

CHEMICALS LIMITED

Pharmaceutical Division

The Brow Burgess Hill West Sussex RH15 9NE
Telephone Burgess Hill 6011 (STD 044 46)
Cables Scherichem Burgess Hill
Telex 87577

Schering

To: Wholesale Chemists
The Ethical Buyer

Your ref

Our ref WNC/CC

June 1975

Dear Sir

With respect to your order for Primodos, please find enclosed a copy of a letter which is being sent to all General Practitioners, Gynaecologists, and Family Planning doctors in your area.

Although the existing packing slip states that Primodos should only be used for secondary amenorrhoea of short duration not due to pregnancy we will also be attaching a special warning label, as quickly as possible, to all packs supplied.

It is anticipated that supplies of these labels will be available during the next few days. An announcement will appear in trade journals on 13 June to inform Retail Chemists of the availability of labels and to offer supplies for existing stocks on request.

Yours faithfully
SCHERING CHEMICALS LIMITED

W N Crothers
Sales Manager

Enc

Appendix 5.

Copy of Page 21 of the Sex Hormone Synopsis with warning sticker attached

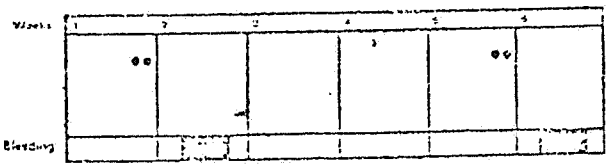
Amenorrhoea

Secondary amenorrhoea of short duration

In the early months of secondary amenorrhoea of functional origin, withdrawal bleeding resembling normal menstruation can be induced by synthetic ovarian hormones.
Note: Pregnancy must first be excluded.

Primodos 1 tablet on each of two consecutive days. Bleeding usually follows in 3-6 days (rarely as long as 10 days). If successful, the treatment should be repeated twice, each time 3 days before the date of the next expected menstruation.

In the rare case in which bleeding does not follow the administration of **Primodos** (usually when the amenorrhoea has lasted 6 months or longer), a careful search for organic disease should be made before giving further hormonal treatment, which should be as for primary amenorrhoea.



WARNING
Not to be taken during pregnancy
A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities. Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant.

PRIMODOS

New text for U.K. data sheet 6.6.75

PRESENTATION

Each orange, sugar-coated tablet contains 10mg norethisterone acetate and 0.02 mg ethinyl oestradiol.

USES

Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy. In the absence of pregnancy it is possible to produce a withdrawal bleeding within 3 to 6 days or, in exceptional cases, after 10 days.

DOSAGE AND ADMINISTRATION

One tablet to be taken on each of two consecutive days.

CONTRA-INDICATIONS, WARNINGS, ETC.

Contra-indication: Not to be taken during pregnancy

A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities.
Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant.

Special precautions: In the rare case in which bleeding does not follow the administration of Primodos (usually when the amenorrhoea has lasted six months or longer), a careful search for organic disease should be made before giving further hormonal treatment, which should be as for primary amenorrhoea.

Side-effects: Rarely, nausea may occur.

Pharmaceutical precautions

Store in cool, dry conditions, away from sunlight: shelf-life five years.

Legal category S4B

Package quantities Foil strips of 2 and 20 tablets

Further information Nil

Product Licence Number 0053/5027

Appendix 7.

PRIMODOS

New text for U.K. packing insert 6.6.75

Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy. In the absence of pregnancy it is possible to produce a withdrawal bleeding within 3 to 6 days or, in exceptional cases, after 10 days.

DOSAGE

1 Primodos tablet to be swallowed whole on each of two consecutive days.

WARNING: NOT TO BE TAKEN DURING PREGNANCY

A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities.
Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant.

Entry for Primodos in ABPI Data Sheet Compendium for 1976

PRIMODOS*

Presentation Each orange, sugar-coated tablet contains 10 mg norethisterone acetate and 0.02 mg ethinyl oestradiol.

Uses Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration, not due to pregnancy. In the absence of pregnancy it is possible to produce a withdrawal bleeding within three to six days or, in exceptional cases, after 10 days.

Dosage and administration One tablet to be taken on each of two consecutive days.

Contra-indications, warnings, etc

Contra-indication. Pregnancy.

Warning: A possibility exists of an association between the use of Primodos during early pregnancy and an increased incidence of congenital abnormalities

Because of this possible hazard, Primodos must not be taken unless it is certain that the patient is not pregnant.

Special precautions: In the rare case in which bleeding does not follow the administration of Primodos (usually when the amenorrhoea has lasted six months or longer), although the patient is not pregnant, a careful search for organic disease should be made before giving further hormonal treatment, which should be as for primary amenorrhoea.

Side-effects: Rarely, nausea may occur

Pharmaceutical precautions Store in cool, dry conditions, away from strong sunlight; shelf-life five years.

Legal category S4B.

Package quantities Foil strips of 2 and 20 tablets.

Further information Nil.

Product licence number 0053/5027.

ATTACHMENT 4

cc: FKP
SJW
WNC
BK
JA

MIMS,
Haymarket Publishing Limited,
Medical Division,
Regent House,
54/62 Regent Street,
London W1A 4YJ.

PB/RAB
5th June, 1975.

Dear Sirs,

Please note that the following addition should be made to the entry for Primodos:

"Contraindication - Pregnancy"

Yours faithfully,

P. Bye BA, MB, MRCS, DCH.
Senior Medical Adviser

Mims

Haymarket Publishing Ltd., Regent House, 54-62 Regent Street, London W1A 1YE. Telephone 01-439 1247

Dr. P. Bye, BA, MB, MRCS, DCH,
Pharmaceutical Division,
Schering Chemicals Limited,
The Brow,
Burgess Hill,
West Sussex,
RH15 9NE.

13th June 1975.

Dear Dr. Bye,

Thank you for your letter.

In view of the fact that the indications for Primodos specifically exclude pregnancy, I feel it is unnecessary to add a contraindication of pregnancy to this product.

Yours sincerely,

F.J. Wilson (Mrs), B. Pharm. MPS.
Editor.

Mrs F.J. Wilson, B.Pharm., MPS.,
Editor,
MIMS,
Haymarket Publishing Ltd.,
Regent House,
54-62 Regent Street,
London, W1A 4YJ

26th June, 1975

PT/MJ

Dear Mrs Wilson,

Thank you for your letter telling me that you do not see the necessity to specify pregnancy as a contraindication to the use of Primodos in MIMS. You may not be aware of the recent events concerning products like Primodos, which were formerly used for pregnancy testing, but which we have for several years not recommended for that purpose. The Committee on Safety of Medicines has recently stated that because there is a suspicion that they can cause foetal abnormalities, such products should not be used as pregnancy tests, and because it is well known that very many doctors are continuing to do so we feel that we should take all reasonable steps to deter them. We agree that the contraindication of pregnancy is implicit in the stated uses of Primodos, but since such an implicit statement in our own literature previously has failed to stop the use of Primodos as a pregnancy test, it seems that it should be made explicit in MIMS as elsewhere.

We feel sure that manufacturers of similar products will ask you to make similar changes in there own entries in MIMS, and we ask you to comply with our own request.

Yours sincerely,

A.G. Pitchford P. Bye

MIMS

Haymarket Publishing Ltd., Regent House, 54-62 Regent Street, London W1A 1YJ. Telephone 01-439 1247

9th July, 1975.

A. G. Pitchford, Esq.,
Schering Chemicals Ltd.,
Pharmaceutical Division,
The Brow,
Burgess Hill,
West Sussex,
RH15 9NE.

Dear Mr. Pitchford,

Thank you for your letter. I was aware of the situation currently concerning products such as Primodos, and their application in pregnancy testing, but I felt that such a contraindication as pregnancy was obvious from the indications.

It is necessary for MIMS entries to be as brief as possible and while I would not wish to economise on space at the expense of clarity or safety, I do wish to avoid repetition of information.

We have just changed the indications of Amenorone to include the phrase 'where pregnancy has been excluded', which was agreed between myself and Roussel as adequately covering the situation. If you are agreeable, I should be happy to amend the wording for Primodos indications similarly. Perhaps you could let me know by Monday, 14th July.

Yours sincerely,

pp RS Rabbett.

Mrs F. J. Wilson,
B.Pharm. MPS,
EDITOR.

Mrs F.J. Wilson, B.Pharm., MPS.,
Editor,
MIMS,
Haymarket Publishing Ltd.,
Regent House,
54-62 Regent Street,
London, W1A 4YJ

AGP/KN 10th July, 1975

Dear Mrs Wilson,

Thank you for your letter dated 9th July, 1975 concerning the MIMS entry for Primodos.

In compliance with your requirement for brevity we agree that inclusion of the phrase, "where pregnancy has been excluded" which you have suggested, will provide an adequate clarification of our recommendations.

Yours sincerely,

A.G. Pitchford, M.B., Ch.B.,
Medical Director.

cc. JA

Mrs. P.J. Wilson, B. Pharm., M.P.S.,
Editor,
Mims,
Haymarket Publishing Ltd.,
Regent House,
54 - 62 Regent Street,
LONDON,
W1A 4AB

PB/jh 14th June, 1978

Dear Mrs. Wilson,

I have just had a telephone call from Mr. Otley of the C.S.M. informing me that he has discussed further with you the problem about the entry in Mims for Primodos, and that the following text is acceptable to both of you:

"Secondary amenorrhoea of short duration. C/I: pregnancy must be excluded."

This version is satisfactory as far as we are concerned, and I should be grateful if you would make the change in future issues.

Yours sincerely,

P. Bye, B.Sc., M.B., M.R.C.P., F.R.C.P.
Senior Medical Adviser

BATT

LP1

Department of Health and Social Security
Medicines Division Finsbury Square House
33-37a Finsbury Square London EC2A 1PP
Telex 883669
Telephone 01-638 6020 ext

Miss H M Barker
Head of Medical Services
Schering Chemicals Limited
Pharmaceutical Division
The Brow
BURGESS HILL
West Sussex RH15 9NE

Your reference
HMB/LR
Our reference
PLR/0053/5027
Date
23 October 1975

Dear Miss Barker

PRIMODOS 10 mg TABLETS

In our letter of 22 September 1975 we agreed to vary the product licence of right referred to above provided that a warning that the product was not to be taken during pregnancy was included as part of the entry in MIMS. You will no doubt be aware that Mrs Wilson, editor of MIMS, has objected to the inclusion of the warning in the terms stated on grounds of uniformity and lack of space.

Upon reconsideration, the indications which now appear in MIMS "eg "Secondary Amenorrhoea of short duration, where pregnancy has been excluded" are satisfactory.

I am copying this letter to Mrs Wilson for her information.

Yours sincerely

E J NICHOLAS

ATTACHMENT 5

58

Department of Health & Social Security,
Medicines Division,
Finsbury Square House,
33-37a Finsbury Square,
LONDON, EC2A 1PP.

RAW/RB

25th January, 1978

Dear Sirs,

Owing to the falling demand for our products:

Endografin (PLR 0053/5022)
(20 x 10 ml ampoules)

Primodos (PLR 0053/5027)
(x 2 and x 20 tablets)

Primolut Depot (PLR 0053/5031 - 250 mg)
(PLR 0053/5032 - 500 mg)
(250 mg 1 ampoule x 1 ml)
(500 mg 1 ampoule x 1 ml)

Urografin 45% (PLR 0053/5042)
(20 x 20 ml ampoules)

we have decided to discontinue marketing the preparations given above. Except in the case of Primolut Depot, where packs of 3 and 20 will remain, these represent deletions from our product range. We are writing to request that our Product Licences of Right should be terminated for those products or presentations given above.

Yours faithfully,

R. A. Wiseman,
PhD.,LRCP.,MRCS.,
DObstRCOG.,DTM&H.,
Medical Director.

ATTACHMENT 6

MR JUSTICE BINGHAM: Yes, Mr Weitzman.

MR WEITZMAN: May it please your Lordship, in this matter I appear with my learned friend Mr Anthony Bano for the Plaintiffs. The Defendants are represented by my learned friends Mr Richard Rougier, Mr Gavin Lightman and Mr Michael Spencer. My Lord, in each of these two cases the Plaintiffs are a mother and child. In the first case the infant Plaintiff, whom I will call, if I may, "D", was born on the 15th May, 1975, so that he is now 7. In the second case the infant Plaintiff "R" was born on the 4th June, 1968 and is now 14. I should mention to your Lordship that for reasons unconnected with the case the infant "D" is a ward of court, and the present application is made with the consent of the Family Division.

My Lord, the writ in the first case was issued on the 19th September, 1977, and in the second case on the 19th December, 1978, and in June, 1980 the cases were ordered to be heard together. The date for hearing of the cases has been fixed as the beginning of October, 1982. However, our present application is for leave now to discontinue the actions pursuant to Order 21, Rule 3 of the Rules of the Supreme Court.

My Lord, in order to explain the reasons which lead us to make the application and to satisfy the Court that it is not contrary to the interests of the infant Plaintiffs I must first briefly state the nature of the claims. Each infant was born with certain physical malformations. In the case of the infant "D" the malformations included a heart defect and the condition known as hypospadias. The infant "R" was born with a complex defect of the heart. In each case the mother had taken a pregnancy test early in the pregnancy. The test was manufactured by the Second Defendants and marketed in the United Kingdom by their associated English company, the First Defendants, where it was known as Primodos. It consisted of two tablets, each containing 10 milligrams of norethisterone acetate and 0.02 milligrams of ethinyl oestradiol. These are synthetic sex hormones. The tablets were to be taken on successive days. If vaginal bleeding did not then occur the inference was that the subject was pregnant.

My Lord, these mothers were in fact pregnant when they took the test with the infant Plaintiffs. The Plaintiffs' case is that the ingestion by the mothers of Primodos adversely affected the development of the foetus and so caused the malformations to which I have referred. In order to succeed in their present claims it would be essential for the Plaintiffs to establish as a matter of probability that Primodos, when given to a pregnant woman, materially increases the risk that her offspring will be born with a congenital malformation. The proof of that proposition depends essentially on the evaluation of expert evidence. The expert evidence is concerned with three main areas of enquiry, but the primary field of investigation on which proof of the Plaintiffs' case must ultimately depend is in the discipline of epidemiology, that is the comparative study in samples of population assembled in various ways of the incidence of a disease or defect among those exposed to the proposed causative agent and those not so exposed. There have been many studies published concerned with the relative incidence of congenital malformations, among those exposed to various

synthetic or exogenous sex hormones whether taken, as in the present case, as a hormone pregnancy test or as support therapy in cases of threatened miscarriage or as oral contraceptives. Those studies have to be evaluated to assess the reliability of the data incorporated in them, the presence or absence of confounding factors which may produce apparent but artificial associations, and for the statistical significance of any associations observed. That evaluation can only be made with the help of expert evidence. Indeed, as your Lordship ruled in earlier interlocutory proceedings, the published studies can only be received in evidence as part of the material on which the opinions of the expert witnesses are based. This whole area of enquiry has been the subject of reports from a considerable number of expert witnesses, whose reports have been exchanged between the parties.

At the outset of the case the expert evidence available to the Plaintiffs' advisers appeared to indicate that there was a reasonable prospect of establishing as probable the existence of a causal association between Primodos and congenital malformations, although the association indicated was of a different order of magnitude from that which, for example, established the teratogenic effects of thalidomide. However, as the expert evidence has accumulated we have been driven to the conclusion that the totality of that evidence does not afford any real possibility that we can establish that there is such an association. We have set out the evidence on which we have reached that conclusion and our process of reasoning in considerable detail in a written opinion, a copy of which has been supplied to your Lordship and which we believe you have had an opportunity to consider.

MR JUSTICE BINGHAM: Yes, I have read that.

MR WEITZMAN: And so we do not propose, unless there is any particular aspect of the case on which we can assist further, to repeat what is set out in the written opinion now. We should, however, say something about two other fields of enquiry which have been considered by the expert witnesses. One of those fields concerns the bioclinical mechanisms by which we have postulated that Primodos might cause congenital defects. These mechanisms are concerned primarily with the causation of hypostadias, although we have fairly recently suggested a possible mechanism for the causation of cardiac defects. The controversies between the experts in this area are discussed in the written opinion, and it is clear that scientists of distinction are not agreed whether or not the mechanisms proposed afford a possible explanation of how Primodos might cause congenital malformations. But we have been driven to the conclusion that on the whole of the biochemical evidence before us, and in the absence of the requisite epidemiological evidence the hypothesised biochemical mechanisms are not capable of establishing that Primodos does cause malformations.

We have also, my Lord, considered the evidence relating to experiments in which the constituents of Primodos and other exogenous hormones have been administered to various animals in various dosages, and once again this evidence is considered in detail in the written opinion. We belive it is common ground among the experts that one cannot reliably extrapolate from the effect of an agent on animals to its effect on humans.

Agents which are teratogenic when given to some animals are not so in others or in humans and, conversely, the fact that an agent does not affect animals does not mean that it cannot affect humans, so animal experiments are of limited probative value. However, the Defendants have themselves carried out a large number of animal experiments and those experiments and the published results of other experiments have been reviewed by distinguished experts in this field, who conclude that they afford no evidence that Primodos is teratogenic, certainly not in the low dosage used in hormone pregnancy tests. In spite of some evidence that sex hormones given to animals in high dosages can have certain teratogenic effects, consideration of the evidence of animal experiments as a whole does not in our view lend any substantial support for the Plaintiffs' case.

In the end, therefore, we felt obliged to conclude that as the evidence stands today there is no reasonable prospect -- indeed, no real prospect -- that we can establish as a matter of probability that Primodos causes congenital malformations. In those circumstances we have had no alternative but to apply that the present action should not proceed to trial. However, we do not wish the actions to be dismissed. We ask instead that they may be discontinued. The reason that we seek that course is this. The scientific enquiry with which we are concerned includes areas of study in which the frontiers of knowledge have advanced and are likely to continue to advance rapidly. While the evidence available to us today does not enable us to advise that the present actions due to begin in October have a reasonable or real prospect of success, we cannot exclude the possibility that within the next few years scientific advances may throw a new light on the problem. In those circumstances it is conceivable that others born with congenital malformations in similar circumstances might be able to bring successful actions. The present infants will not for a number of years be barred by the Limitation Act from bringing a fresh action, and if the present action were discontinued they would be able to do so, subject to the conditions which the Court impose. If, however, the present action is dismissed, their cause of action will have gone and they alone will be barred from seeking a remedy available to others of like ages should the postulated scientific advances occur. That, in the circumstances I have outlined, would in our submission be a grave prejudice to the infant Plaintiffs, and we therefore ask that our application be granted. We recognise of course that the Defendants should be protected from any possible unjust consequences of that course, and we therefore accept that if your Lordship were to grant our application it should be upon the term that the Plaintiffs bring no fresh action upon the same cause of action without the leave of the Court. We would ask you not to impose a condition that before starting a fresh action with such leave the costs of the present action should be paid. We say that because the Court which has to grant leave can consider the justice of any application and itself impose any terms that seem appropriate as to costs.

My Lord, those are the matters on which we rely in support of this application, and unless there are any particular aspects of the case on which at this stage I can assist your Lordship further, it is all I desire to say in opening the matter.

MR JUSTICE BINGHAM: Thank you, Mr Weitzman. Yes, Mr Rougier.

MR ROUGIER: My Lord, in the submission of the Defendants the proper course in a matter such as this would be for the case to be dismissed, or rather I should say the "cases", since there are in all four involved, rather than for the Plaintiffs to be given leave to discontinue. I say that for the following reasons. In our submission the rule makes it plain, and your Lordship has had an opportunity, I understand, of considering the rules, so I need not elaborate on that, that your Lordship has an unfettered discretion as to which course would be proper in the interests of justice to adopt, and there is no rule in particular either of practice or substance whereby a plaintiff could always get leave to discontinue before he had actually brought his adversary to Court for the purposes of the trial of the action. And even if that were so, we would respectfully remind your Lordship that apart from an application by the Plaintiffs to adjourn which was granted, this case was due actually to start yesterday, and in our submission the Plaintiffs should not be in any better position where that tactical exercise is concerned merely because they sought and obtained an adjournment. Therefore, in our respectful submission, my Lord, your Lordship's jurisdiction and discretion is unfettered by rules of practice, and since effectively the Plaintiffs in such an application are accepting that they cannot realistically hope to succeed we submit that really the only relevant criterion for your Lordship to consider is whether, by allowing the Plaintiffs to discontinue, injustice would be done to the Defendants. My Lord, for that we rely on the two cases of Young v. B.M.A. (1977) 2 All England Reports, and Castanho v. Brown & Root (1981) Appeal Cases, and I understand that there is the list of authorities which your Lordship has had an opportunity of considering.

MR JUSTICE BINGHAM: Yes.

MR ROUGIER: Then I do not think it necessary to refer your Lordship to them again. My Lord, in our submission in summary very great injustice would be done to the Defendants if this action were other than dismissed in the present circumstances. We say this by reason of two matters which we would submit are of general principle and two which are particular to these actions. In so far as general principles are concerned, this is a case of enormous magnitude and of enormous importance, not only of course to the Plaintiffs but also to my clients. The allegations which were made in support of the Plaintiffs' cases were such as impugn my clients' reputation, conduct and the soundness of their product, and had they succeeded the cost in terms of not only finance but also reputation would have been incalculable. Not unnaturally, literally millions of pounds have been spent by my clients and hours and hours, possibly years of effort and research since these actions were started in order to prepare themselves and to find out scientifically on which side the truth lay. Now in plain terms, my Lord, if (and I have nothing but, if I may say so, respect for the responsible way in which the Plaintiffs and their advisers have approached the realities of the matter) but if it be the fact that they concede that they have no reasonable prospect of success, in our respectful submission it would not be right that the Defendants should have the possibility of these allegations being rescuscitated and hanging over their heads for many

years to come, when one remembers that one of the Plaintiffs is I think but seven years of age with another fourteen to run before the limitation period expires.

Secondly, we would submit, my Lord, that to allow the Plaintiffs to discontinue in these circumstances would obviously create a very dangerous precedent, not only where my clients are concerned but in similar cases which people may seek to bring in the future.

Turning, my Lord, to the particular matters, we submit that it was only if the Plaintiffs could put before your Lordship some evidence which would give credence and substance to what can otherwise only be a hope that the time scientific knowledge would turn and begin to flow in their favour, that they could put before your Lordship some indication that this was so, but, on the contrary, all the -- I say the experiments which my clients have either conducted or commissioned tend to show -- of course one could never prove anything absolutely -- but they tend to show that the further the frontiers of knowledge are extended the more likely, in our submission, it is that the Defendants' contentions will be reinforced by the advance of science, and in so far as the question of timing is material of course that can never change.

My Lord, there is a point which I put very far from the forefront of my submissions but I feel it right to make it, that as we interpret, or a possible interpretation of Section 13 of the Legal Aid Act, 1974, in order for a successful party who is unassisted to be entitled to make any claim either for his costs or part of them against the Legal Aid Fund it would be necessary that proceedings would have to be decided in his favour. We venture, with great respect, to doubt whether a successful application to discontinue would amount to a decision in favour of the other party. The result of that would be, my Lord, that if your Lordship acceded to my learned friend's application the Defendants would thereby be precluded even from having the chance of recovering some part of these very substantial costs which they have already incurred.

My Lord, on the final matters, may I say this, that if your Lordship nevertheless were minded to accede to the Plaintiffs' application the conditions which we would submit would be right and proper for your Lordship to attach to it are not only that the Plaintiffs should not without leave of the Court bring any further action but we would seek also for an order that they should not do so without first paying the Defendants' costs. Unless I can assist your Lordship further, I have nothing more to say.

MR WEITZMAN: My Lord, may I make four points in reply to what has fallen from my learned friend's lips. It is of course true that had it not been for an adjournment granted by your Lordship this case would have been due to begin as a trial I think yesterday. My Lord, I do not think it is suggested -- I would certainly resist any such suggestion -- that the adjournment was in any way dictated by a desire to achieve a tactical advantage. It was dictated by the nature of the accumulating evidence and the need to deal with it. My Lord, perhaps the most significant point made by my learned friend is that it is unfair that the Defendants should have these claims hanging over their heads. If this were a unique case, in the sense that these were the

only Plaintiffs who had the possibility of such a claim, one would see very great force in that contention. The fact is that there are a number of other possible claimants in this and other jurisdictions, and the order that your Lordship makes today cannot one way or the other affect the possibility that such potential claimants will in due course, if the evidence becomes available to support the making of such a claim, bring actions. My Lord, therefore first of all the Defendants will inevitably in the nature of the circumstances have that possibility hanging over their heads, and, secondly, it is precisely that feature of the case that would make it unfair, in our submission, that if such an eventuality occurred these infant Plaintiffs should be shut out from the remedy which would be available to others.

My Lord, so far as the question of the application for costs out of the Legal Aid Fund is concerned, so far as that is a material matter to mention, I know that your Lordship will have in mind the provisions of Section 7(6)(b) of the Legal Aid Act, 1974, which in our submission make it clear that a consideration of that sort is not to affect the exercise of your Lor ship's discretion in the present application.

My Lord, in relation to the final matter raised by my learned friend, that any order giving leave to discontinue should include a provision that before starting the action, the fresh action, the Plaintiffs must pay the costs of the present action, one envisages as a possibility a situation in which others have brought a successful action and then these infant Plaintiffs, the matter in a sense having been established, come to Court to seek their remedy, but should that arise the Court granting leave can impose whatever terms it thinks just. We would invite your Lordship to say that it would not be right to fetter that jurisdiction at the present moment. I do not know if I can assist your Lordship further .....

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J U D G M E N T

(As approved by the Judge)

MR JUSTICE BINGHAM: In these actions there are (effectively) two Plaintiffs, one of them aged 7 and the other aged 14. Both claim damages alleging that as a result of pregnancy testing drugs taken by their mothers during pregnancy they were born with serious congenital defects. The drug in question is named Primodos, which was manufactured by the Second Defendants and marketed in this country by the First Defendants.

That brief introduction is enough to suggest a comparison with the very well-known tragedy involving thalidomide, and it is quite plain from what I have already been told and seen in the pleadings that these actions are of a very serious kind. There is, however, one important difference between these cases and the thalidomide cases. There the question was one of whether the drug companies involved had been negligent in their manufacture and promotion of thalidomide. Here, in these actions, there is that issue but also an issue not present in the thalidomide cases, namely a serious issue whether this drug has had any causal connection whatever with the defects from which the children suffer.

Now the matter comes before me today because Mr Weitzman, appearing for the Plaintiffs, seeks leave to discontinue the actions on the ground that the Plaintiffs and their advisers have concluded that the actions have no reasonable or real prospect of success. There are accordingly two questions that fall to be answered.

First, should the Plaintiffs be permitted to bring the proceedings to an end? Ordinarily, of course, that would be a question for the Plaintiffs, but it is not simply a question for the Plaintiffs here because there are children involved and the Court is always concerned that those not old enough to conduct their own affairs should not be prejudiced by anything done in their name.

The second question which arises is: If the Plaintiffs should be permitted to bring their proceedings to an end,

then in what manner and on what terms should the case be brought to an end?

So far as the first question is concerned, Mr Weitzman has outlined the grounds which lead him and his colleagues to conclude that on the evidence available the actions stand no reasonable prospect of success, and I have had the advantage of reading an opinion in which that conclusion was elaborated, being an opinion running to over 120 pages, analysing the issues and the evidence and reviewing the matter in a great deal more detail than has been possible today. Various things are plain. First of all, the subject matter, particularly on the causation aspect, is of very great complexity indeed. The Defendants have, I believe, submitted reports by no fewer than 28 experts on that subject. A great deal of published research has been done over the years, and for purposes of this case a good deal, as I understand, of experimentation on animals has been carried out. I cannot pretend to any detailed understanding of the technical issues in the case. It is, however, right to say that having read and I hope absorbed the opinion which Counsel for the Plaintiffs have written, I have no reason whatever to doubt the validity of the conclusions which they reach. It is also right to say that in a situation of this kind the Court places very considerable reliance on the considered view of experienced Counsel and solicitors representing plaintiffs, who will undoubtedly have the interests of those plaintiffs very closely at heart. Accordingly I consider it right, in the light of the conclusions which the Plaintiffs' advisers have reached, that this action should come to an end. I would also mention that the Plaintiffs are legally aided, and one should perhaps acknowledge the very responsible decision which, in the light of that fact, the Plaintiffs' advisers have taken.

So I go on to the second question: How and by what means should the action be brought to an end? The Plaintiffs seek leave to discontinue on terms which would leave them free, in the event of a scientific revolution on the subject, to proceed again. The Defendants understandably resist that application and ask that the action should be dismissed. Mr Rougier points out that the Defendants have faced a very substantial and serious challenge to their reputation and conduct. They have spent vast sums and made extensive preparations for contesting the action. They are ready to contest the action and are confident that if it were to go to trial now or in the autumn,

when it is now due to be tried, they could defeat the claims. Mr Rougier also points out that the threat of these actions has been hanging over the heads of the Defendants for a long time, and he submits that they are entitled to be freed from that threat. In a nutshell, he says, the Defendants are prepared to fight now. If they did contest the action now they are confident that they would succeed, and it is unfair that the claims should be preserved with the risk of further presentation when the climate appeared more propitious for the Plaintiffs.

It is I think clear as a matter of law that the issue that arises is one for the discretion of the Court, there being no right to discontinue by plaintiffs at this stage. It is also perhaps right to mention Mr Rougier's submission that if the action were not dismissed he would be prejudiced in an application which he seeks to make in due course against the Legal Aid Fund for the costs which he has expended and which will in the circumstances be irrecoverable against the Plaintiffs.

I approach this matter with very considerable sympathy with the Defendants' contentions. I remind myself that justice must be done to them as well as to the Plaintiffs, and if the Plaintiffs were adults I think it is exceedingly probable that I should accede to Mr Rougier's submission at least to the extent of giving leave to discontinue on the most stringent terms. As it is, I must bear in mind that these Plaintiffs are children, and that although the claims, particularly in one case, are of some age since the child is now 14, nonetheless the claims are still well within the statutory limitation period governing claims by children. Accordingly I conclude that the Plaintiffs should have leave to discontinue, subject to the term that no further action should be brought in respect of the complaints the subject matter of this action without the leave of the Court on such terms as the Court may then impose. I shall not myself impose any term as to the previous payment of costs, although it may be that any Court to whom application was made would impose that term.

The effect of that order is not to shut out the Plaintiffs absolutely. It is open to them to apply in the future in the event of a scientific revolution or a marked change in the circumstances. I should, however, make it clear that for leave to be given on any future occasion a very strong case indeed would have to be made out by the Plaintiffs to show that

it was just for the matter to be re-opened, and the Court would have to be satisfied that no unreasonable prejudice to the Defendants would accrue. I think it very unlikely that leave to the Plaintiffs would be given, but I think that it is in all the circumstances just that the door should be kept open to that very limited extent. I would add that while I express no conclusion in the absence of the Law Society as to the legal construction of the section of the Legal Aid Act governing an application by the Defendants for costs against the Fund, my preliminary view is that in these circumstances the action would be held and could properly be held to have been decided favourably to the unassisted party. That is not, as I have stressed, a final conclusion but a preliminary view.

I shall hear any application that Mr Rougier wishes to make about the costs of this matter, but would just say this. The action has been listed under initials, so far as the children are concerned, and I hope that in any report that appears of this matter very great care will be taken to ensure that the names of the children do not in any way appear in a manner that would enable them to be identified. I know that the Press will fully co-operate on this matter, as they always do.

MR ROUGIER: My Lord, on the question of costs I think I can safely say that my learned friend and I have reached agreement as to what should be the proper order. As a matter of history, my Lord, one might well imagine that certain interlocutory battles went up and down the ladder, some of them getting as far as the Court of Appeal. The Defendants sought to have certain matters tried as preliminary issues and they lost on that and they were required to pay the Plaintiffs' costs, and what has been agreed, subject to your Lordship's overriding discretion, is that the Plaintiffs shall not enforce those orders for costs in their favour without leave of the Court, and that for the rest I would seek an order that the Plaintiffs pay the Defendants' costs, but again such order not to be enforced without the leave of the Court -- the adult Plaintiffs.

MR JUSTICE BINGHAM: The Plaintiffs not to enforce their order for costs in their favour without leave.

MR ROUGIER: And for the rest an order for costs in my favour, but again I am not to enforce it without the leave of the Court.

MR JUSTICE BINGHAM: The order for costs against the adult Plaintiffs.

MR ROUGIER: The adult Plaintiffs.

MR JUSTICE BINGHAM: Not to be enforced without leave.

MR ROUGIER: Yes.

MR JUSTICE BINGHAM: I suppose there is no objection under the Legal Aid Act to the first of those orders, is there?

MR ROUGIER: No, I think there is not because it is in fact a way of saving the expense of taxation, as it were.

A

MR JUSTICE BINGHAM: Yes.

MR ROUGIER: So it can only save money. My Lord, your Lordship did say that there were two Plaintiffs. There are in fact of course four, because the adult Plaintiffs have, albeit small, substantive claims of their own.

B

MR JUSTICE BINGHAM: Yes, but I am afraid I was concentrating on the effective .....

MR ROUGIER: Of course, we all were but, my Lord, as a matter of discontinuance it is all four.

MR JUSTICE BINGHAM: That is right, there shall be leave to all the

C

Plaintiffs, yes.

MR ROUGIER: I am very much obliged, my Lord.

MR WEITZMAN: Then I do not think that I can add anything to what has been said. It seems to me that that is an appropriate way in all the circumstances for your Lordship to deal with the costs.

D

MR JUSTICE BINGHAM: Yes, I am very grateful. The order on costs will therefore be that the Plaintiffs shall not enforce the order for costs in their favour made in the interlocutory proceedings without the leave of the Court, and that there be an order for costs in favour of the Defendants against the adult Plaintiffs in each action, such order not to be enforced without the leave of the Court.

E

MR BANO: My Lord, the present application comes before your Lordship as an interlocutory matter and I would ask your Lordship to certify for two Counsel in relation to that matter.

MR JUSTICE BINGHAM: I shall certainly certify for two Counsel, if it is necessary.

F

MR ROUGIER: I am not legally aided. It has got nothing to do with me.

MR JUSTICE BINGHAM: For purposes of Legal Aid taxation.

MR BANO: My Lord, I think on our side we should ask formally for your Lordship to order a Legal Aid taxation in relation to the costs of the action.

G

MR JUSTICE BINGHAM: Yes, Legal Aid taxation of the Plaintiffs' costs; certificate for two Counsel for the Plaintiffs. I am very grateful to you both; thank you very much.

H

SANOFI

Response to Hormone Pregnancy Tests Questions

The Commission on Human Medicines (CHM) Expert Working Group on Hormone Based Pregnancy Tests (HPTs) concluded in 2017 that the available scientific evidence does not support a causal association between the use of HPTs during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital abnormalities.

Sanofi heritage companies ceased the commercialisation of its hormone pregnancy test products over 40 years ago and have no evidence to submit to the Review that can add to the conclusions reached by the CHM Expert Working Group.

Other

The following manufacturer was invited to respond and declined as they have not marketed or supplied Hormone Pregnancy Tests in the UK.

- Alinter (Wallace)