

Hormonal pregnancy tests (including Primodos) and possible association with birth defects

Call for evidence

Launch date 25 March 2015

Respond by end of June 2015

To	Healthcare professionals, healthcare organisations, researchers, women who took oral hormonal pregnancy tests (including Primodos) between 1958 and 1978 (and their children and immediate families)
Issued	25 March 2015
Enquiries to	email: hpts@mhra.gsi.gov.uk

1. Summary

1.1 The Medicines and Healthcare products Regulatory Agency (MHRA) is inviting interested individuals and organisations to provide any information they consider relevant to a possible association between the use of oral hormonal pregnancy tests and adverse effects on the pregnancy or subsequent birth defects in the child. All evidence provided will be reviewed by a group of independent experts. A report of the group's findings will be published at the end of the review process.

2. About hormonal pregnancy tests

2.1 Hormonal Pregnancy Tests (HPTs) first became available in the UK in the late 1950s and were also licensed for a number of other gynaecological conditions. The most frequently used HPT, Primodos, contained norethisterone acetate (10mg) and ethinylestradiol (0.02mg) and one tablet was prescribed to women suspected to be pregnant to be taken on two consecutive days. In women who were not pregnant, bleeding would occur a few days after the tablets were taken.

2.2 A number of other HPTs which contained similarly high doses of synthetic hormones (a progestogen in combination with an estrogen) were also available in the UK, including Amenorone, Amenorone Forte, Disecron, Menstrogen, Norone, Norlestrin, Norlutin A, Orasecron, Paralut, Pregnot and Secrolyl.

2.3 In the late 1960s a number of studies were published that found an association between use of a HPT and birth defects in the child. Other studies found no association. The introduction of

alternative tests for pregnancy resulted in the gradual phasing out of HPTs.

2.4 By the early 1970s Primodos was indicated only in secondary amenorrhoea (absence of menstruation). In the mid-1970s it was contraindicated for use in women known to be pregnant. In 1978 Primodos was voluntarily discontinued by the manufacturer for commercial reasons. Similar action was taken with the other HPTs. A more complete background on HPTs can be found in Annex 1.

2.5 In 2014 the MHRA reviewed the key published evidence on the possible effects of HPTs, such as Primodos, taken by the mother during pregnancy and the subsequent development of the child. The report of this review concluded that the data are not sufficient to conclusively prove the existence of an association between the use of Primodos (or any HPT) and birth defects and that there may be other factors, possibly not even known at the time of study which mean an adverse outcome would have been observed regardless of whether the medication had been administered. The report can be viewed below.

[Assessment of historical evidence on Primodos and congenital malformations \(355Kb\)](#)

3. About this call for evidence

3.1 Following parliamentary interest in this issue, a Backbench Business Committee debate took place on 23rd October 2014 and a transcript of the debate can be viewed below.

[Oral Hormone Pregnancy Tests - Backbench Business Committee debate on 23rd October 2014](#)

3.2 The Commission on Human Medicines (CHM) has endorsed the need for a review of all the evidence relating to oral HPTs and has agreed terms of reference for an expert group comprising independent experts in relevant scientific disciplines.

3.3 The review is not a political enquiry intended to demonstrate liability, but to examine the evidence to assess whether there are grounds for accepting a link between the use of HPTs and the conditions experienced by some.

3.4 To be sure that all the available evidence is reviewed the MHRA is conducting a search for all relevant documents. As part of this process, evidence is being sought from any individual or organisation who has information they wish to submit for consideration by the experts during the review.

4. Evidence sought

4.1 The MHRA welcomes any evidence that people wish to provide, but examples of the kind of information that may be useful include:

- Any unpublished information from clinical trials, observational data or other scientific studies

relating to the effects of use of HPTs in pregnancy or on the developing fetus

- Citations for published information from clinical trials, observational data or other scientific studies relating to the effects of use of HPTs in pregnancy or on the developing fetus
- Published or unpublished information on the outcome of intentional or inadvertent exposure to progestogens and estrogens (at any dose) during pregnancy
- Any evidence of the impact of local or national restriction or withdrawal of HPTs from use, particularly in relation to the incidence of birth defects.
- Any information on the use of HPTs considered to be possibly associated with effects on pregnancy or the foetus. We would encourage using the Yellow Card reporting site to confidentially send us any personal or confidential information. The Yellow Card reporting site can be found at the address below:

<http://www.mhra.gov.uk/yellowcard>

Please include as many details as possible, and particularly the type (brand) of HPT, the dates of pregnancy, when in the pregnancy the HPT was taken, the outcome of the pregnancy and anything else you think is important.

We also encourage you to provide the following in the “additional information” field of the Yellow Card form:

- Information on previous and subsequent pregnancies
- further details of any birth defects or adverse effects on the pregnancy following exposure to a HPT during pregnancy

Should you wish to add/attach any additional records/notes please email these to: yellow.card@mhra.gsi.gov.uk quoting the reference number for your report to ensure that your records can be linked.

If the online Yellow Card reporting site cannot be used or people would prefer not to use it, we would suggest sending us (via e-mail or post):

- Copies of medical records showing historical use of a HPT, the dates of pregnancy, when in the pregnancy the HPT was taken and the outcome of the pregnancy
- Copies of medical records or letters from healthcare professionals relating to any birth defects which are considered related to HPTs (including their diagnosis and treatment)

5. How to respond

5.1 We would welcome any information you wish to provide up to the end of June 2015. If you are not submitting information via the Yellow Card reporting site, please use the email address that we have set up for this purpose: HPTS@mhra.gsi.gov.uk

5.2 Or send hard copies by post to:

HPTs c/o Expert Committee Support
4-T, MHRA
151 Buckingham Palace Road
LONDON
SW1W 9SZ

5.3 We will make sure that all information provided is included in the review for consideration by the panel.

6. Deadline

6.1 The call for evidence closes on 30 June 2015.

7. Next steps

7.1 As HPTs are no longer on the market, and the companies who marketed these products no longer exist, no regulatory action can be taken in relation to these products. However, the findings of the review may have implications for currently licensed medicines and the Expert Group will advise CHM on this matter.

7.2 The Expert Group will advise the CHM. We anticipate that a report (including a public summary) will be made publicly available once the review is complete.

Freedom of information

The information you send us may need to be published in a summary of responses received and referred to in the published final report of the review.

All information requests will be subject to the Freedom of Information Act 2000 (FOIA 2000), and data provided will not be disclosed if there are relevant exemptions within the FOIA 2000 which apply. If you want the information in your response to the call for information to be kept confidential, you should explain why as part of your response. As a default position, the MHRA normally withholds personal information (such as names and contact details), in line with the requirements of the Data Protection Act 1998. If there is relevant information that you consider can only be shared subject to restriction, please flag this up to us. However please note that we cannot give an absolute guarantee that we will be able to withhold all the information that we are requested to.

Read more information about the [Freedom of Information Act](#).

Annex 1 – background information on HPTs

Scientific and Regulatory environment between 1950s and 1970s

1. Access to pregnancy testing through laboratory confirmation in the 1950s and 1960s was tightly controlled by doctors and generally reserved for use in urgent, medical-priority cases that required differential diagnosis – for example, to distinguish the growth of a normal foetus from that of a tumour. Although immunological test kits became available in the 1960s, they were not available for women to buy from Pharmacies until the 1970s.
2. HPTs became available in the late 1950s and offered a relatively simple method of diagnosing early pregnancy compared with existing methods. The most frequently used HPT, Primodos, contained two hormones - norethisterone acetate (10mg) and ethinylestradiol (0.02mg). One tablet was taken on two consecutive days by women suspected to be pregnant. In women who were not pregnant, a withdrawal bleed would occur a few days later. Other HPTs similarly contained high doses of progestogen and an estrogen.

Regulatory History of Primodos and other Hormonal Pregnancy Tests in the UK

3. After some years of their being available, claims were made by some researchers and patients at the time that HPTs (and Primodos in particular), were associated with an increase in birth defects. In 1967 Dr Isabel Gal informed the Committee on Safety of Drugs (CSD, who later became the Committee on Safety of Medicines, or CSM) that she had conducted a study that identified an association between use of HPTs and spina bifida.
4. CSD considered the study to be flawed and that the findings were not supported by evidence from other studies or data from studies in animals of the effects in pregnancy. Publication of Dr Gal's study in Nature in 1967 was swiftly followed by a number of other studies investigating this alleged association, with inconsistent results.
5. CSM kept this issue under review and in 1969 began its own study of medicines taken by women who gave birth to children with birth defects. Minutes of discussions of the Sub-Committee on Adverse Reactions and the CSM held at the National Archives in Kew suggest that the issues relating to HPTs and a possible link with birth defects were discussed on numerous occasions by the Committees between 1967 and 1978.
6. With time, other non-hormonal methods of diagnosing pregnancy became available and in the early 1970s Schering restricted the indication for Primodos to secondary amenorrhoea (loss of menstrual periods). Similar action was taken for the other HPTs.
7. The preliminary findings of the CSM's study of medicines taken by women who gave birth to children with birth defects became available in 1975 and indicated a statistical, but not necessarily causal, relationship between hormonal pregnancy tests and non-specific birth defects.
8. In June 1975 the CSM wrote to all doctors in the UK via its 'Adverse Reactions' warning leaflet informing them of the preliminary results of their study and the finding for a possible association between HPTs and an increased incidence of birth defects. The CSM recommended that, in

view of the possible hazard, and the availability of alternative methods, doctors should not normally prescribe hormonal preparations for pregnancy tests.

9. In view of accumulating, albeit inconsistent, evidence regarding a possible adverse effect of HPTs on the developing baby, coupled with the increased availability of non-hormonal methods of testing for pregnancy, the CSM also undertook a number of additional precautionary actions to minimise any potential risk. These included:
 - a. removing any remaining indications for HPTs for the diagnosis of pregnancy;
 - b. adding a warning to the outer box and all promotional materials about the possible hazard in pregnancy
 - c. publishing articles in the British Medical Journal (BMJ)
 - d. asking the companies who marketed HPTs to stop promoting them.
10. In November 1977 in response to reports that Primodos was continuing to be used as a HPT, CSM issued a further 'Adverse Reactions' warning leaflet to doctors. This reminded them of the possible hazard and drew attention to the final results of its own study, which confirmed the preliminary finding for an association. The final study report was published in the BMJ. The Alert reiterated the CSM's earlier warning that hormonal tests for pregnancy should not be used.
11. Although Primodos remained available in the UK for use in the treatment of amenorrhoea, it was contraindicated (meaning it should not be used) in pregnancy and in January 1978 it was voluntarily discontinued by the manufacturer (Schering, later Bayer) for commercial reasons. Other HPTs were also discontinued around this time.

Scientific reviews of the data since Primodos and other HPTs were taken off the market

12. Since 1978, a number of studies and reviews of the evidence have been performed, including a review of all available evidence by the WHO in 1982 which concluded that while the results of the more satisfactory investigations suggested that HPTs may be associated with an increased risk of congenital abnormalities, that by no means proved an association.
13. More recently, the MHRA reviewed the key published evidence relating to HPTs and congenital defects, and the report was published on the MHRA website in March 2014. The report concluded that the data are not sufficient to conclusively prove the existence of an association between the use of Primodos (or any HPT) and birth defects and that there may be other factors, possibly not even known at the time of study which mean an adverse outcome would have been observed regardless of whether the medication had been administered.

Licensed medicines containing norethisterone acetate and ethinylestradiol

14. No currently licensed medicine in the UK contains norethisterone acetate and ethinylestradiol at the same dosages as were present in Primodos. However, these hormones remain very common components of a wide range of medicines that are effective in the treatment of

gynaecological disorders, menopausal symptoms, cancer and in contraception.

15. The current World Health Organisation model list of essential medicines includes norethisterone 1mg in combination with ethinylestradiol 35 micrograms as an oral contraceptive and an injection of norethisterone enantate 200 mg/ml as an injectable hormonal contraceptive.
16. No norethisterone-containing products are indicated for use in pregnancy, and most are contraindicated in pregnancy. The regulatory and social environments have changed greatly since the 1970s and as a result no medicines are recommended for use in pregnancy unless considered essential. However, because norethisterone and ethinylestradiol are commonly found in contraceptives, the components of Primodos are not infrequently taken during the early stages of as yet undiagnosed pregnancies due to contraceptive failure.
17. Reflecting the conflicting evidence in the past, product information for a small number of these medicines still contains a warning about the possible risk of congenital abnormalities. However, the product information for the majority of these medicines now state that “the majority of recent studies do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy” and that “the results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect”.