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# Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: a drug utilisation study

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## ABSTRACT

**Purpose** To assess the compliance with the isotretinoin Pregnancy Prevention Programme (PPP) by evaluating the use of prescribed contraceptives among isotretinoin users. The PPP contains a requirement for the use of contraceptive methods for women of childbearing potential.

**Methods** A drug utilisation study was performed using data from a drug prescription database (containing Dutch community pharmacy data) covering a population of 500 000 patients. Contraceptive use in female isotretinoin users and in a reference group of female non-isotretinoin users (aged 15–49 years) was compared using data from 1999 until 2006 in 2-year periods. Descriptive statistics were used.

**Results** Of the female isotretinoin users ( $n = 651$ ), 52%–54% filled prescriptions on contraceptives in strict accordance to the PPP, used before, during, and after discontinuation of isotretinoin, compared with 39%–46% in the reference group. A more liberal approach of a minimum of one prescription for a contraceptive method showed 61%–64% use of contraceptives among isotretinoin users. Similar patterns were seen when data were broken down in age groups. Furthermore, a higher proportion of female patients using isotretinoin prescribed by general practitioners used prescribed contraceptives compared with those receiving isotretinoin by specialists.

**Conclusion** Compliance with the contraceptive use according to a PPP for a teratogenic drug such as isotretinoin is 52%–64%, which is lower than anticipated. Reasons for the low compliance will need to be clarified before further measures can be taken. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS— isotretinoin; contraception; PPP adherence

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## INTRODUCTION

Isotretinoin is a vitamin A derivative used for the treatment of severe acne that has failed to respond to conventional acne therapy.

Dutch studies on the prevalence of acne in general practice showed a range between 30% and 90%, depending on the definition.<sup>1</sup> A study in the UK<sup>2</sup> and a study in Germany<sup>3</sup> show a prevalence of clinical acne in women of 23% and 24%, respectively. Only 10% of both male and female acne patients experience severe acne, defined as having at least 20 papules and/or pustules had used systemic treatment, and <1% of all acne patients ever used isotretinoin.<sup>4</sup>

Because vitamin A derivatives are highly teratogenic in humans, a strict Pregnancy Prevention Programme (PPP) is in place.

Isotretinoin was authorised in the USA in 1982 and in Europe in 1983. In 1983,<sup>5</sup> the first cases of congenital anomalies appeared despite a contraindication for pregnancy because of the teratogenic risk of vitamin A derivatives. Therefore, in 1983, the product information was revised by the Marketing Authorisation Holder (MAH), Roche. Additional steps were taken such as placing a text about teratogenicity in the product information, and letters were sent to prescribers and pharmacists with additional information on the warnings. Worldwide, a PPP was implemented by Roche in 1988. In the USA, this PPP has been amended twice thereafter, in 2001 (System to Manage Accutane Related Teratogenicity [SMART]) and in 2006 (iPLEDGE; a more stringent programme in which prescribers, patients,

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No ethical approval was necessary for this study.

pharmacists, and wholesalers are registered in an online database).<sup>6</sup> In 2003, in Europe, due to the entrance of generic products containing isotretinoin on the market, a regulatory referral was performed to harmonise the indication for isotretinoin as well as the PPP.<sup>7</sup> The prevalence of congenital anomalies with isotretinoin is about 26% in live births.<sup>8</sup> The aim of these PPPs is to avoid pregnancies before, during the use, and 1 month after discontinuation of isotretinoin because of the high risk of congenital anomalies.

A PPP is a risk minimisation measure as defined in the guideline<sup>9</sup> on risk management plans. In this case, the risk on exposure to isotretinoin during pregnancy and indirectly a risk on congenital anomalies should be avoided. Elements of the PPP of isotretinoin are presented in Box 1. The use of contraceptives by female isotretinoin users might provide an indication of the effect of the PPP.

During recent years, cases of *in utero* exposure of isotretinoin have been identified despite the PPP.<sup>10,11</sup> For regulatory authorities, it is important to gain insight in the compliance with the PPP, which is intended to gain 100% avoidance of pregnancies. The use of contraception by female isotretinoin users could be an indication of compliance with the PPP, which can be assessed and quantified in contrast to some of the other elements of the PPP. We performed a drug utilisation study with the data of a Dutch community pharmacies database (IADB.nl) to evaluate the use of contraceptives among female isotretinoin users as main outcome. To measure whether the PPP had effect, the use of contraceptives in female isotretinoin users was compared with contraceptive use in the general population in the same age group. In addition, we evaluated different aspects (e.g. compliance in urban vs. rural areas, innovator product vs. generic formulations of isotretinoin, first prescriber and isotretinoin preceded by prescribed conventional therapy vs. no preceding conventional therapy) that might influence the use of contraceptives and thereby indirectly the adherence to the PPP.

## MATERIALS AND METHODS

### Database

Data of Dutch community pharmacies are obtained from IADB.nl<sup>12</sup>: a database which contains prescriptions of a population of approximately 500 000 individuals from the Netherlands. The data in the database consist of among others personal characteristics (an anonymous identifier, gender, and date of birth) and drug information as Anatomical Therapeutic Chemical (ATC) code<sup>13</sup> of the World Health Organisation, the

dispensing date, the theoretical end date, and the prescriber.<sup>12,14</sup> Dutch patients commonly register with one pharmacy and mainly obtain their prescription medication from this pharmacy, so medication histories of patients can be considered nearly complete.<sup>15</sup>

### Study population

The study covered the period of 1999 to 2006. Both males and females aged 15–49 years using isotretinoin were selected ( $n = 1825$ ).

Isotretinoin users to be included in the study were determined by the first prescription of isotretinoin in the database, which has to be at least 180 days after the date the patient first appeared in the database.

The prevalence rates of male and female isotretinoin users were compared in general and specifically for first-time prescribers of isotretinoin, for example, specialists or general practitioners (GPs).

### Reference population

The population aged 15–49 years in the area covered by the community pharmacies participating in the database during the period 1999–2006.

### Isotretinoin use among female users

We selected in this dataset female patients aged 15–49 years who had received any isotretinoin prescription during the study period. Two-year prevalence of female isotretinoin users was calculated. The ATC code for systemic isotretinoin, D10BA01, was used. The 2-year prevalence was defined as the number of female isotretinoin users who received at least one prescription in a 2-year period divided by the population in that age group.

### Contraceptive use among female isotretinoin users

We selected in this dataset female patients aged 15–49 years who had received any isotretinoin prescription during the study period. In this group of isotretinoin users ( $n = 651$ ), contraceptive use was calculated and compared with the use of contraceptives in the population of female non-users of isotretinoin between 15 and 49 years of age (reference group).

Prescriptive contraceptive methods have been defined as all forms of intrauterine devices (IUDs), hormonal implants, oral contraceptives (including cyproteron acetate/ethinyl-estradiol [CPA/EE]) and depot medroxyprogesterone acetate. The period of use for these contraceptions was considered to be 1 year for the oral and depot contraceptives, 3 years for the hormonal implants, and 5 years for the IUDs.

The use of contraceptive methods among isotretinoin users was calculated by two methods: (i) a liberal method: the number of women who had at least one prescription of a contraceptive in the period described earlier for the different contraceptive methods as the isotretinoin prescription divided by the total number of isotretinoin users and (ii) a strict method, in which the period of contraceptive use has been defined as 30 days before isotretinoin was used, the duration of its use, and 30 days after the use of isotretinoin ended.

The use of contraceptives in the reference group was calculated as the number of women (isotretinoin non-users) in the age group of 15 through 49 years with at least one contraceptive prescription divided by the female population (15–49 years) of the covered area.

### Other variables

Among the female isotretinoin users, we also compared compliance to the PPP related with other variables such as area (rural vs. urban), type of isotretinoin formulation (innovator product vs. generic products), first prescriber of isotretinoin (specialist vs. GP), preceding use of conventional anti-acne medication, and type of contraceptive (CPA/EE vs. others).

- Urban areas are defined as cities with at least 100 000 citizens, and rural areas were all other areas. There have been suggestions of better adherence differences on drug use in rural areas compared with urban areas,<sup>16,17</sup> which triggered the question on the compliance of contraceptives and isotretinoin in these areas.
- The performance with the innovator product Roaccutane® was compared with the performance using generic products of isotretinoin. The innovator and the generic products were determined by the trading product code (hpk in Dutch) number, an identification number for every product that is on the market in the Netherlands that can distinguish different brands.<sup>18</sup> The MAH of the innovator Roaccutane® with long-time experience with a PPP for isotretinoin in contrast with the MAH of generic products of isotretinoin but despite the harmonised European PPP for isotretinoin was considered useful in comparing compliance with the contraceptive use as part of the PPP among these products.
- Contraceptives prescribed for female isotretinoin users with first prescriber of isotretinoin, specialist, or GP were analysed. Isotretinoin may be prescribed by physicians known with the product. A study performed in France<sup>19</sup> showed that GPs did perform less than dermatologists.
- Conventional anti-acne medication was defined as the first-line medication for treatment of acne according to standards for dermatologists and for Dutch GPs.<sup>20</sup> Contraceptive use in female isotretinoin users with prescribed conventional anti-acne medication before isotretinoin use was compared with those without preceding prescriptions of conventional anti-acne medication. Prescription of conventional medication before isotretinoin is part of a guideline,<sup>1</sup> considering PPP as a guideline; therefore, the theory that in case a prescriber did not follow one guideline he or she would also not follow the PPP for isotretinoin.
- Proportion of users of the combination preparation of CPA/EE in the female isotretinoin user group was compared with the proportion of CPA/EE in the reference group. CPA/EE is not licensed as a contraceptive;<sup>21</sup> it is licensed for the treatment of acne in female patients, but it also has contraceptive properties and therefore used as such in daily practice. From literature,<sup>22</sup> it is known that the women with acne will more often use CPA/EE as a contraceptive, despite that it is not licensed for this indication.

### Statistics

Descriptive statistics were used, and calculation of proportions was in percentage with 95% confidence intervals (95%CI), if applicable. Based on these confidence intervals, statistical significant differences with the reference population could be determined.

## RESULTS

During 1999–2006, we identified 1825 isotretinoin users in the IADB.nl database between 15 and 49 years of age. The group of isotretinoin users consisted of 64% male users ( $n=1171$ ) and 36% female users ( $n=651$ ).

The proportion of female isotretinoin users versus male patients was higher with the specialist compared with the GP, 64% and 40%, respectively.

The prevalence of contraceptive use among the female isotretinoin users in both analyses the more strict (52%–54%) and the more liberal (61%–64%) definition and was compared with contraceptive use in the female general population (39%–46%), showing a significant higher proportion of contraceptive use in both isotretinoin groups (see Table 1 and Figure 1).

Rural areas have a better compliance with contraceptive use compared with the urban area (see Table 1). In the periods 2003–2004 and 2005–2006, there is

Table 1. Data from the female population aged 15–49 years in the database for different variables

	1999–2000	2001–2002	2003–2004	2005–2006
Isotretinoin and contraceptives (PPP)*, <i>n</i> (%), [95%CI]	121 (54, [47–61]) <sup>†</sup>	108 (54, [47–61]) <sup>†</sup>	103 (54, [47–61]) <sup>†</sup>	83 (52, [44–60]) <sup>†</sup>
Isotretinoin and contraceptives <sup>‡</sup> , <i>n</i> (%), [95%CI]	142 (64, [57–70]) <sup>†</sup>	124 (62, [56–69]) <sup>†</sup>	116 (61, [54–67]) <sup>†</sup>	98 (62, [54–69]) <sup>†</sup>
Reference group and contraceptives, <i>n</i> (%), [95%CI]	80 778 (45.7 [45.5–45.9])	80 412 (44.6 [44.4–44.8])	80 814 (43.0 [42.8–43.2])	79 944 (39.1 [38.9–39.3])
Age (years), <i>n</i> (%)				
15–24				
Isotretinoin and contraceptives (PPP)	47 (62)	48 (57)	44 (55)	36 (50)
Reference group and contraceptives	28 846 (54)	28 646 (56)	28 968 (56)	28 139 (51)
25–34				
Isotretinoin and contraceptives (PPP)	51 (61)	44 (61)	38 (53)	29 (63)
Reference group and contraceptives	30 894 (54)	29 353 (56)	28 607 (55)	27 496 (51)
35–49				
Isotretinoin and contraceptives (PPP)	23 (37)	16 (37)	21 (55) <sup>†</sup>	18 (44) <sup>†</sup>
Reference group and contraceptives	20 392 (25)	21 681 (26)	22 372 (25)	23 320 (23)
Innovator versus generic isotretinoin, <i>n</i> (%)				
Innovator with contraceptives	121 (54)	108 (54)	63 (56)	48 (66) <sup>§</sup>
Generic with contraceptives	–	–	57 (55)	44 (45)
Urban areas versus rural areas, <i>n</i> (%)				
Urban				
Isotretinoin users and contraceptives	78 (53)	66 (54)	58 (49)	41 (43)
Reference group and contraceptives	46 660 (56)	44 715 (55)	43 544 (54)	41 401 (52)
Rural				
Isotretinoin users and contraceptives	43 (56)	42 (55)	45 (63)	42 (67) <sup>¶</sup>
Reference group and contraceptives	33 291 (57)	33 480 (57)	33 279 (56)	32 306 (53)

CI, confidence interval; PPP, Pregnancy Prevention Programme.

\*Strict contraceptive use in accordance with PPP.

<sup>†</sup>Statistically significantly higher compared with the reference group.

<sup>‡</sup>Liberal contraceptive use.

<sup>§</sup>Statistically significantly higher compared with the comparator group generic formulations.

<sup>¶</sup>Statistically significantly higher compared with the urban isotretinoin users group and to the rural reference group.

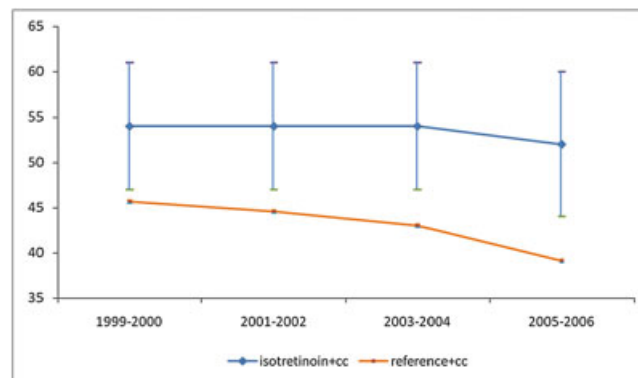


Figure 1. Distribution (%) of prescribed contraceptives in isotretinoin users according to the strict definition of the PPP and controls. PPP, Pregnancy Prevention Programme

even an increase in compliance in the rural areas compared with the urban areas. Compared with a reference group of contraception users, the urban female isotretinoin users have a lower proportion of contraception use from 2003 onward (see Table 1). Rural female isotretinoin users with contraception have a better

compliance than that of a reference group of rural contraception users from 2003 onward (see Table 1).

Use of contraceptives with the innovator product versus the generic products containing isotretinoin was compared. The generic isotretinoin formulations came on the market from 2003 onward; only the last

2-year periods have data for comparison and show a statistically better performance in the innovator product in the period 2005–2006 (see Table 1).

The compliance of contraceptive use with the origin of first prescriptions of isotretinoin was compared. The proportion of contraceptive users in the female population was significantly lower in the specialist group compared with the GP group, 63% versus 71%, respectively.

The use of prescribed contraceptives in female isotretinoin users who had prescriptive conventional treatment of acne preceding use of isotretinoin was compared with isotretinoin use without preceding prescribed conventional acne therapy. The proportion of prescribed contraceptives in the group of female isotretinoin users with preceding conventional anti-acne treatment was 66% (61–71 [95%CI],  $n=236$ ) compared to 41% (32–50 [95%CI],  $n=46$ ) in the group without preceding conventional anti-acne medication, which is statistically significantly higher. The compliance of specialists and GPs in the group of female isotretinoin users with preceding prescriptive conventional anti-acne medication and contraception was similar, 52% and 48%, respectively. However, in the group of female isotretinoin users without preceding prescriptive conventional anti-acne medication and contraception, the compliance of specialists was higher than GPs, 63% and 37%, respectively.

The proportion of CPA/EE of the contraceptives used in the isotretinoin user group is 59.9%. In the reference group, the use of CPA/EE is below 9.6% of the contraceptive use.

## DISCUSSION

In this study, a significantly higher use of prescribed contraceptives was found among female isotretinoin users using contraceptives in accordance with the PPP (52%–54%) as well as with the liberal use of a minimum of one prescription of a contraceptive method (61%–64%) compared with the use of prescribed contraceptives in the female general population, reference group (39%–46%). Compliance to contraceptive use among female isotretinoin users was also better in rural versus urban areas as well as with preceding therapy of conventional anti-acne treatment compared with no preceding therapy. Furthermore, female patients using isotretinoin prescribed by general practitioners had a better performance compared with those receiving isotretinoin by specialists.

Limitation of the study is the lack of information on barrier methods, such as condom use, and on sterilisation of the female isotretinoin users. Therefore, there

will be underrating of the contraceptive methods for both isotretinoin users and the reference group. For example, for 2008, Statistics Netherland<sup>23</sup> shows that a proportion of 3% of all Dutch women are sterilised and that 9% used a condom for contraception. Further limitation might be the lack of explanations for the lower compliance with contraceptive use among female urban isotretinoin users and contraception even lower than the reference group.

The strength of this study is the comparison of contraceptive use among isotretinoin users compared with contraceptive use among non-isotretinoin users. In addition, several aspects related to prescribing isotretinoin and contraceptives are studied, for instance, compliance related to first prescribers and preceding conventional anti-acne medication.

The PPP for isotretinoin contains among others a requirement of the use of contraceptive measurements for women of childbearing age. Preferably two methods should be used, one of which should be a barrier method. Because of this condition for prescribing isotretinoin to women of childbearing age, the use of prescribed contraceptives in accordance with the PPP would be ideally expected to have an almost 100% coverage in addition to the barrier methods. In the end, it seems that the PPP has received some attention because of the 10%–20% higher usage of prescribed contraceptives in the female isotretinoin users group compared with the female general population.

The proportion of women using prescribed contraceptive methods in the Dutch population by Statistics Netherlands<sup>18</sup> was 45% in 1998 and 46% in 2003. According to these data, the use of prescribed contraceptives reference group is comparable with the use in the general Dutch population, justifying female non-users of isotretinoin in the IADB.nl database as reference.

A recent study by Teichert *et al.*<sup>24</sup> showed at the stringent analysis of contraceptive use in female isotretinoin user population a comparable proportion of contraception use with that in our analysis. The study by Teichert *et al.* and our study are complementary and provide a good insight in the compliance of contraception use among female isotretinoin users in the Netherlands.

Despite the fact that CPA/EE should not be used solely as a contraceptive, women with acne will use this combination preparation of CPA and EE as conventional anti-acne medication and contraceptive and will continue using it as contraceptive during use of isotretinoin despite the recommendation to stop after treatment of 3 to 4 months. If CPA/EE would be excluded as a contraceptive, the contraception

compliance in female isotretinoin users would be very low. Regulatory authorities could use this as an opportunity to inform prescribers and pharmacists on this phenomenon and the substantial off-label use of CPA/EE as contraceptive.

Prescribers not following the guidelines for treatment including the one on acne might also tend to neglect the PPP of isotretinoin. This might be an explanation for the smaller proportion of contraceptive use among isotretinoin users without preceding conventional anti-acne medication. Although it would be expected from the overall better compliance of GPs regarding contraceptive use in female isotretinoin users, the compliance of GPs in the subgroup of female isotretinoin users without preceding conventional anti-acne treatment was much lower compared with specialists.

Prescribed oral contraceptives have a pearl index of 1%–2% and therefore do not guarantee 100% pregnancy prevention. The pearl index is used for contraceptive methods and is a rate determined by the number of unintentional pregnancies related to 100 women years. Moreover, during the first week after the pill-free period, missing pills seem to occur,<sup>16</sup> which can result in an unplanned pregnancy. In addition, it was shown that even women with fairly good contraceptive compliance sometimes experienced unplanned pregnancies.<sup>25</sup> These data are a reason to use a second contraceptive method, preferably a barrier method.

The data suggest that education of prescribers and pharmacists involved in the PPP might need specific attention and focus to enhance the performance and adherence, and also reminders that the PPP is mandatory might be helpful. Pharmacists, among others, with the task of controlling prescriptions might feel specifically responsible for the requirement of the restricted prescription of isotretinoin for female users of 30 days and the fact that there is a time limit on the prescription of 7 days. Together with prescribers, they might take a role in creating awareness of these requirements.

In the database, there are more females receiving prescribed medication than males are. In contrast, isotretinoin has been more prescribed for male patients (0.57%) than for female patients. This could be due to higher prevalence of severe acne in men compared with women or because of the teratogenicity that isotretinoin will be less prescribed for women (0.27%).

Compliance with use of contraceptive methods as part of risk minimisation measures such as a PPP for teratogenic drugs is lower than anticipated. Adherence

to the PPP is a joint responsibility of regulatory authorities (to develop a good programme and create awareness), prescribers (to inform patients and perform specific investigations), pharmacists (to monitor adherence), and ultimately patients to adhere to specific requirements. Reasons for this low compliance should be clarified first to implement improvements or before further measures can be taken.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## KEY POINTS

- Compliance with the contraceptive measures in the PPP is much lower than that aimed at 100%.
- Prescribers, patients, and pharmacists have a joint responsibility for the performance of the PPP.

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Box 1. Elements of the isotretinoin Pregnancy Prevention Programme.

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- Contraindication pregnancy
  - Information for patient (both males and females) regarding teratogenicity
  - Educational material for patient (only female)
  - Contraception brochure
  - Informed consent form for women of childbearing potential to sign
  - Pregnancy tests before, during, and after treatment of isotretinoin
  - Supply restrictions of isotretinoin for women of childbearing potential to 30 days per prescription, and a prescription has a validity of 7 days
  - At least one method of contraception; preferably two methods, one of which is a barrier method
  - Isotretinoin should only be used by the person for which it is prescribed
  - Patients using isotretinoin should not donate blood up to and including to at least 1 month after discontinuation
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