

Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review

H.J.M.J. Crijns,*† S.M. Straus,*‡ C. Gispen-de Wied* and L.T.W. de Jong-van den Berg†

*Medicines Evaluation Board, The Hague, the Netherlands

†Department of PharmacoEpidemiology & Pharmacoeconomics, Graduate school of SHARE, University of Groningen, Ant Deusinglaan 1, 9713 AV Groningen, the Netherlands

‡Department of Medicinal Informatics, Erasmus Medical Center, Rotterdam, the Netherlands

Summary

Correspondence

L.T.W. de Jong-van den Berg.

E-mail: l.t.w.de.jong-van.den.berg@rug.nl

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Most of the publications on isotretinoin, pregnancy and compliance with the pregnancy prevention programme (PPP) originate from North America. Information specific for the European situation is very limited. The aim of this study was to identify publications describing the use of isotretinoin in humans and the compliance with the PPP in Europe, a systematic search in Medline and Embase was conducted using the terms 'isotretinoin, pregnancy (and Europe)'. Furthermore, a manual search in publications was performed. A total of 17 publications were identified. Publications consisted of case reports of exposed pregnancies, surveys among dermatologists or pharmacists and database studies evaluating compliance with the PPP. The studies and surveys dealt with groups of patients exposed to isotretinoin before or during pregnancy and/or compliance with the isotretinoin PPP. Where the information was provided, in 6–26% of cases isotretinoin was prescribed in full accordance with the PPP. Pregnancy incidence was seen in 0.2–1.0 per 1000 women of childbearing age using isotretinoin. Between 65% and 87% of these pregnancies were terminated. This review of studies in Europe performed to date shows failures in the implementation of the PPP. Therefore, the isotretinoin PPP must be scrutinized to identify whether new measures should be taken or whether the failures in the implementation need to be corrected. New measures should take into account the definition of the ultimate goal of a PPP and the acceptable burden. In the meantime, stakeholders could make a start with adjustments in the implementation of the PPP by taking responsibility and enhancing the performance by explicit instructions, monitoring the performance and adjusting, if necessary.

Isotretinoin was authorized in the U.S.A. in 1982 and in the EU in 1983 and was marketed by Roche as Roaccutane® for the treatment of severe acne. In 1983 the first reports of congenital malformations appeared¹ despite warnings about the teratogenic risks in pregnancy. The retinoic acid embryopathy described by Lammer *et al.*² has a relative risk of 26%. This embryopathy consists of craniofacial, cardiac, thymic and central nervous system malformations. The relative risk of congenital malformations due to isotretinoin exposure during pregnancy is comparable to the relative risk for thalidomide.

In 1988 the marketing authorization holder implemented a pregnancy prevention programme (PPP) for oral isotretinoin, which was included in the product information worldwide. In the U.S.A., studies on the compliance with the PPP were performed by research institutes,^{3,4} by the Food and Drug Administration (FDA)⁵ and by Roche. Because of a lower than expected compliance a more strict PPP for isotretinoin was

implemented in the U.S.A. in 2002, 'SMART', and an even stricter PPP was implemented in 2006, 'iPledge'.

In 1997, recommendations for the prescribing and dispensing of isotretinoin were strengthened in France. In 2001 the first generic formulation of isotretinoin became available. Currently there are at least 70 generic oral isotretinoin formulations on the market in Europe (communication between EU member states). Because of differences in the PPPs between the different isotretinoin-containing products, a harmonization procedure for all isotretinoin-containing products was approved by the European Commission in October 2003. During this harmonization procedure not only was the PPP harmonized but also the indication for use was amended to a stricter second-line indication for oral isotretinoin. Currently in Europe, isotretinoin is indicated as a treatment for severe forms of acne resistant to adequate courses of standard therapy with systemic antibacterial medication and topical therapy.

The literature search revealed that most of the publications on isotretinoin, pregnancy and compliance with the PPP originate from North America. Information specific for the European situation is very limited. The aim of the current study was therefore to perform a review of publications on the use of isotretinoin in pregnancy and compliance with the PPP in Europe.

Materials and methods

A search was performed in Medline with the Medical Subject Headings (MeSH) terms 'isotretinoin, pregnancy, Europe' and 'isotretinoin, pregnancy'. Embase was searched with the terms 'isotretinoin, pregnancy'. The Medline searches identified 10 and 302 publications, respectively, on 31 August 2009. On the same date, the Embase search identified a total of 641 publica-

tions. A language selection was made for publications in English, French, German or Dutch. Other selection criteria were studies, case reports, oral isotretinoin, and human data. The searches were supplemented with manual analyses of references of the leading publications and all identified European publications dealing with systemic use of isotretinoin and birth defects.

Identifying studies on compliance with the use of oral isotretinoin, surveys and case reports resulted in 17 European publications, which are discussed below.

Results

A total of 17 publications were identified,^{6–22} consisting of case reports of exposed pregnancies, surveys among dermatologists or pharmacists and database studies evaluating the compliance with the PPP. The results are presented in Tables 1 and 2.

Table 1 Identified studies and surveys

Author(s)	Title	Country	Year	Type	Source
Autret <i>et al.</i> ⁶	Isotrétinoïne (Roaccutane) chez la femme en âge de procréer: insuffisance de suivi des recommandations de prescription	France	1997	Study	Questionnaires to pharmacovigilance organizations and pharmacists
Holmes <i>et al.</i> ⁹	The prescription of isotretinoin to women: is every precaution taken?	U.K.	1998	Survey	Questionnaire survey of dermatologists
Källén ¹⁰	Restriction of the use of drugs with teratogenic properties: Swedish experiences with isotretinoin	Sweden	1999	Study	Medical Birth Registry for infants in Sweden
Autret-Leca <i>et al.</i> ⁷	Roaccutane chez la femme en âge de procréer: étude de l'impact du renforcement des recommandations de prescription	France	2000	Study	All pregnancies from several sources in France, such as pharmacovigilance centres, Roche and TIS and sample of drug prescriptions
Wildfang <i>et al.</i> ¹¹	Isotretinoin in Denmark – 20 years on	Denmark	2002	Survey	Questionnaire survey of dermatologists
Dutronc <i>et al.</i> ¹²	Modalités de prescription et de surveillance de l'isotrétinoïne en Côte d'Or: étude prospective chez 67 femmes en âge de procréer	France	2004	Study	Questionnaire to randomly selected pharmacies
Bensouda-Grimaldi <i>et al.</i> ⁸	Isotrétinoïne: suivi de l'application des recommandations des prescriptions chez les femmes en âge de procréer	France	2005	Study	All pregnancies from several sources in France, such as pharmacovigilance centres, Roche and other MAH and TIS and sample of drug prescriptions
De Santis <i>et al.</i> ¹³	The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity	Italy	2007	Study	TIS database
Jeanmougin <i>et al.</i> ¹⁴	Aide au bon usage de l'isotrétinoïne en pratique libérale: observatoire prospectif de 1263 patients acnéiques	France	2009	Study	Prospective observational, national, multicentre study
Schaefer <i>et al.</i> ¹⁵	Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy	Germany	2010	Study	TIS database with prospective and retrospective cohorts compared with controls

MAH, marketing authorization holder(s); TIS, Teratology Information services.

Table 2 Identified case reports

Author(s)	Title	Country	Year	Source	Features of infant	Exposure to isotretinoin
Van Maldergem <i>et al.</i> ¹⁸	Morphological features of a case of retinoic acid embryopathy	Belgium	1992	One case	Female fetus with enlarged and elongated head, low-set microtic ears, hypertelorism and a flat and depressed nasal bridge. Ventriculomegaly of lateral ventricles and cerebellar hypoplasia. Dextrocardia, with enlarged heart, ventricular septal defect and single truncus arteriosus	Three months before conception and during first months of pregnancy
Heckel <i>et al.</i> ¹⁹	Tératogénicité des rétinoïdes. Un cas et revue de la littérature	France	1993	One case	A healthy female infant was delivered	Conception probably took place 10 days after stopping isotretinoin
Benifla <i>et al.</i> ¹⁶	Fetal tissue dosages of retinoid. Experimental study concerning a case of isotretinoin (Roaccutan) administration and pregnancy	France	1995	Therapeutic abortion in isotretinoin pregnancy and determination of concentrations in fetal tissues	Terminated pregnancy at 17 weeks' gestation: macroscopic normal fetus. Tissue concentrations of isotretinoin and its metabolites showed transplacental crossing of isotretinoin and/or its metabolites	Isotretinoin was used before and during pregnancy
Pilorget <i>et al.</i> ²⁰	Embryopathie liée à l'isotrétinoïne (Roaccutan®). A propos d'une observation	France	1995	One case	Agnesia of both external ears, a systolic cardiac murmur and paralysis of the right facial nerve and poor spontaneous movements	Isotretinoin use until 1 week before presumed conception date
Pons <i>et al.</i> ¹⁷	Dosages maternels et foetaux de rétinoïdes. A propos de 2 cas d'exposition à l'isotrétinoïne (Roaccutan®)	France	1996	Two cases of which one was already reported in the publication of Benifla <i>et al.</i> ¹⁶	First case, see Benifla <i>et al.</i> ¹⁶ Second case, concerns a fetus with a spina bifida and myelomeningocele. Again, high concentration of isotretinoin and its metabolites in the fetal tissue	Isotretinoin use during first trimester of pregnancy in both cases
Dos Santos <i>et al.</i> ²¹	Tératogénicité de l'isotrétinoïne	France	1998	Two cases	First case, male infant with plagiocephaly and asymmetric face with ptosis of the right eyelid. Later on the child had psychomotor retardation Second case, male infant with microcephaly and psychomotor retardation	First case, oral isotretinoin use during first trimester of pregnancy Second case, topical isotretinoin use on chest and back during the first month of pregnancy
Giannoulis <i>et al.</i> ²²	Isotretinoin (Ro-Accutane) teratogenesis. A case report	Greece	2005	One case	No cephalic skull up to the frontal bone, absent stomach, oesophagus atresia and small ventricular septal defect	Isotretinoin use until 16th week of gestation
De Santis <i>et al.</i> ¹³	The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity	Italy	2007	One case	Complex cardiopathy and bilateral anotia	Isotretinoin use until the 5th week of pregnancy

Taking into account the selected publications, France contributed more than half the publications ($n = 10$) of which nine were in French; all other publications were in English.

Studies and surveys

The identified studies and surveys among dermatologists or pharmacists deal with groups of patients exposed to isotretinoin before or during pregnancy and/or compliance with the PPPs for isotretinoin. Parts of the results of these studies and surveys are presented in Tables 3 and 4.

Three of the French studies were performed by the group of Autret-Leca *et al.*^{6–8} within the same database and showed a development over time.

In France, the incidence of pregnancies with isotretinoin use remains stable between 0.2 and 1.0 per 1000 women of childbearing age. In the last of this group's publications, by Bensouda-Grimaldi *et al.*,⁸ the covered period was divided because of the authorization of generic formulations of isotretinoin in 2001.

In the first study,⁶ a total of 318 pregnancies were reported over a period of 9 years (1987–1995). During and after isotretinoin use, in 84% contraception was not prescribed or was prescribed with poor compliance.

In the second study,⁷ 37 pregnancies were reported over a 22-month period (March 1997 to December 1998). Restricted measures for pregnancy prevention came into force in March 1997 and this study was to evaluate the new procedures. In the third study,⁸ 103 pregnancies exposed to isotretinoin occurred over a 4-year period (1999–2002).

The second part of these three studies concerned prescription surveys on the recommendations of the PPP current at that time. Questionnaires were completed by the pharmacist while interviewing female patients with isotretinoin prescriptions.

In the first study,⁶ 230 pharmacies were selected and 102 actually participated in the questionnaire survey. A total of 173 questionnaires were analysed. The prescriptions covered 3 months (range 1–16 months) for isotretinoin and in 13 cases (8%) were accompanied with a prescription for a contraceptive.

In the second study,⁷ of the 310 selected pharmacies 105 pharmacies actually participated in the questionnaire survey. A total of 165 questionnaires were filled out. In 27 cases the contraceptive method did not fulfil the PPP criteria, for instance Diane[®] was prescribed in 19 cases and in 17 cases the contraceptive method was poorly described.

In the third study,⁸ 45 pharmacies participated and 68 questionnaires were analysed. In 47% the prescription concerned Roaccutane[®] and in the other cases generic formulations of isotretinoin.

A questionnaire survey with dermatologists practising in Scotland⁹ was performed. Sixty-four of the 90 dermatologists completed the questionnaire of which there was a similar proportion of men and women, and clinical experience and age. Patients were asked about the possibility of a pregnancy in 95% of the women older than 16 years and in 70% of the women younger than 16 years. In patients younger than 16 years, in only 41% was a pregnancy test routinely performed. Verbal and written advice on avoiding pregnancy was given in 97% of cases. In general, oral contraceptives were considered an adequate form of contraception, for 75% of the physicians progestogen-only or an intrauterine device (IUD) was also suitable and for 15% barrier methods such as condoms were also acceptable. In 67% the dermatologists asked the general practitioner to prescribe an oral contraceptive and in 27% Dianette[®] was suggested. With 79% of the physicians isotretinoin was started after at least 1 month of oral contraceptive use. In only 6% of cases was a pregnancy test performed at each visit. Ten per cent of the physicians did not warn their patients to avoid pregnancy for 1 month after discontinuation of isotretinoin; a number of physicians recommended avoidance for 2 months after stopping isotretinoin.

A Swedish study¹⁰ was performed on the Medical Birth Registry for infants born during 1982 through 1989. In Sweden isotretinoin may be prescribed only on a named patient basis. A total of 301 pregnancies were identified in women who had received isotretinoin. There were 173 infants (including eight twins) whose mothers had been treated with isotretinoin before pregnancy, of which two infants had major birth defects: one child with a ventricular septum defect and

Table 3 Information on pregnancies associated with isotretinoin use

	Autret <i>et al.</i> ⁶	Autret-Leca <i>et al.</i> ⁷	Bensouda-Grimaldi <i>et al.</i> ⁸	Schaefer <i>et al.</i> ¹⁵
Period	1987–1995	March 1997–December 1998	1999–2002	1993–2008
Pregnancy incidence (per 1000) ^a	0.2–0.7	0.4–0.8	0.3–1.0/0.3–0.8 ^b	
Terminated pregnancies (%)	81	65	87	76
Pregnancies during treatment with isotretinoin (%)	16	49	29	47 ^c
Pregnancies during first month of termination of isotretinoin treatment (%)	33	22	45	

^aPer 1000 women of childbearing age using isotretinoin. ^bPeriod was divided because of authorization of generic formulations of isotretinoin in 2001. ^cDatabase of Teratology Information Services, requests for information.

Table 4 Results from studies on the compliance of the isotretinoin PPP

	Autret <i>et al.</i> ⁶ (n = 173)	Holmes <i>et al.</i> ⁹ (n = 64)	Autret-Leca <i>et al.</i> ⁷ (n = 165)	Wildfang <i>et al.</i> ¹¹ (n = 132)	Dutrone <i>et al.</i> ¹² (n = 67)	Bensouda-Grimaldi <i>et al.</i> ⁸ (n = 68)	De Santis <i>et al.</i> ¹³ (n = 35)	Jeanmougin <i>et al.</i> ¹⁴ (n = 55 ⁺)
Mean age, years (range)	24 (12–47)		26 (±8)		24 (15–45)	25 (14–45)		21 (±7)
Prescription by dermatologists (%)	93	100 ^a	89	100 ^a	89	90		100 ^a
Contraception in accordance with PPP (%)		75	70	85	72	78	57	99
Contraception not used (%)	28		12		11	4		
Correctly prescribed isotretinoin (%) ^b	14		18			6	26	
Contraception continued during first month of termination of isotretinoin (%)			93			82	57	96
Pregnancy test before start of isotretinoin (%)	29	55	85	60	78	96	37	98
Pregnancy test at 5 weeks after termination of isotretinoin (%)			64			62		
Signed acknowledgment form (%)		95	87			88		
Monthly pregnancy test (%)		6	88 ^c	32		96		99

PPP, pregnancy prevention programme. ^aSurvey of dermatologists. ^bIsotretinoin prescribed in full accordance with the PPP for women of childbearing potential. ^cEvery second month instead of monthly.

one child with preaxial polydactyly. Of the 132 infants (six twins) who were born before isotretinoin was given, one child had a cleft lip and palate. Only three women were identified who had used isotretinoin during pregnancy; all three infants were normal. These three women did not use oral contraceptives or IUDs during isotretinoin treatment.

In Denmark¹¹ a questionnaire was circulated to 185 dermatologists 20 years after the introduction of isotretinoin; 132 questionnaires were returned with a response rate of 71%. Post-treatment advice on avoiding pregnancy differed from 1 month in 29% to 2 months in 42%, 3 months in 15% and more than 3 months in 11%.

A prospective survey was performed in France in 2001, and published in 2004,¹² in 50% of the 182 pharmacies of the Côte d'Or. Of these pharmacies, 37 (41%) collected prescriptions of isotretinoin. Sixty-seven patients filled out a questionnaire of whom 74% lived in an urban environment and 26% lived in a rural or semi-rural environment. The prescriber of isotretinoin was a dermatologist in 60 cases (89.5%). Isotretinoin was prescribed for acne in 66 cases and in one case for cutaneous lupus. In 53 (79.1%) cases the prescription was the first prescription, in 12 cases (17.9%) it was the second prescription and in two cases (3%) it was the third prescription. Five women did not have a pregnancy test. The teratogenic risk was known to 48 women (71.6%) through friends before consulting the physician. Seventeen women (25.3%) never received an information leaflet. Of the women who had read the information before, 87% had the pregnancy test in accordance with the PPP. In contrast, of the women who read the information later or who did not receive an information leaflet, 57% had a pregnancy test in accordance with the PPP ($P = 0.007$). Thirty-eight women (56.7%) were not aware that contraception should continue after stopping isotretinoin; however, they continued the contraception for even more than 1 month (median of 3 months).

The Italian study¹³ evaluated the system of the isotretinoin PPP in Italy and was performed by Telefono Rosso (TR), a member of the European Network of Teratology Information Services (ENTIS). During the period from July 2002 to October 2005, 52 patients contacted TR, including 19 requests (36.5%) for information pre-conception, 29 pregnancies (55.8%) including four pregnancies concerning paternal exposure. The 29 pregnancies consisted of pregnancies in which the patient discontinued isotretinoin 1 month or more before pregnancy. Data from 35 of the 52 women could be used for evaluation with the following additional results (not presented in Table 4): indication was not followed correctly in 10 women (28.6%), claim of not receiving clear and precise information on teratogenicity in five women (14.3%), and treatment started on 2nd or 3rd day of menstruation in nine women (25.7%). In addition to the study, a case was reported of a child with complex cardiopathy and bilateral anotia born to a woman using isotretinoin until the 5th week of pregnancy (see Table 2).

A prospective observational study was performed in France¹⁴ covering the period October 2005 through January

2007. A total of 1263 patients were included of whom 56% were male ($n = 709$) and 44% were female ($n = 554$); 296 dermatologists participated of whom 72% were female. The mean age of the physicians was 48 ± 7 years. A pregnancy test 5 weeks after stopping isotretinoin was not evaluated. One month before starting treatment with isotretinoin 548 women used effective contraception. An oral contraceptive was used by 98% and the remaining 2% used an implantable progestogen, IUD or were menopausal. In 13% of the women contraceptives were temporarily interrupted with a maximum duration of one cycle.

The most recent study was performed in Germany¹⁵ in which pregnancies occurring during isotretinoin use recorded between 1993 through 2008 were evaluated on their pregnancy outcome. In total 230 information requests on oral isotretinoin were received during the covered period by the Teratology Information Service (TIS). In 108 of these 230 cases, isotretinoin was used during the period of 1 month prior to conception and/or during pregnancy. If information on contraceptive measures was available ($n = 69$), 69.9% did not use contraceptive measures and 30.4% ($n = 21$) used contraception which failed. All patients did not use two complementary contraceptive measures as recommended by the isotretinoin PPP. The 91 known pregnancy outcomes were compared with controls, comprising prospective enrolled pregnancies of women who have been exposed to nonteratogenic agents during the study period. There were 5.5% spontaneous abortions vs. 10.1% in the control group, 75.8% elective terminations vs. 1.9%, and 18 live births (19.8%) including a pair of twins vs. 88.0%. Three (16.9%) of the 18 live born infants had congenital malformations vs. 8.5%, consisting of major birth defects 5.6% ($n = 1$) vs. 3.7% ($n = 12$).

Case reports

Eight case reports and their outcomes are presented in Table 3, one of which was a case report presented in a publication on a study. The case reports originate mostly from France with single case reports from Italy, Belgium and Greece.

In two case reports of French origin,^{16,17} concentrations of isotretinoin and its metabolites were determined in fetal tissue. The first case was described in both publications.

Discussion

A systematic literature review was performed in Medline and Embase on studies and case reports using MeSH terms isotretinoin, pregnancy and Europe. A total of 17 publications were identified of which 10 were studies, including two surveys and seven were publications of case reports. The studies evaluated compliance with the isotretinoin PPPs in these countries. A common conclusion of all the studies and surveys was that compliance was regarded as insufficient and that the PPP should be strengthened. The case reports indicate that preg-

nancies occurred despite the fact that a PPP for isotretinoin was in place.

A limiting factor in the three French studies could be the fact that pharmacists performed the interviews. Pharmacists are participants in the control process and the answers might also concern their compliance with the programme. Therefore, possible bias cannot be excluded.

Due to the different periods of data collection and the changes over time in the PPPs, the introduction of generic drugs, and the regulatory referral of isotretinoin, a comparison of the results of the studies and surveys and comparison of the routine risk minimization activities in different countries is difficult.

This review reveals deficiencies in the implementation of the isotretinoin PPP. Poor compliance was shown among others by failure of contraceptive measures causing 30% of the pregnancies. Responsibility for this poor compliance seems to lie with prescribers, patients, pharmacists and also the regulatory authorities.

It can be discussed whether Diane-35[®] or Dianette are acceptable contraceptives in this situation. These medicinal products are authorized for the treatment of acne in women and also have contraceptive action. Prescribing these products for contraceptive use should be considered carefully, because of the high risk of thrombosis, which is even higher than in third-generation oral contraceptives.

The efficacy of the PPP in the prevention of pregnancies is important as more and more teratogenic drugs become available for use, for example lenalidomide and thalidomide. However, these drugs have mostly oncological indications and are not likely to be prescribed to women of childbearing age. Isotretinoin on the other hand is prescribed for an aesthetic problem, which is not life-threatening or causing disability in the age group of childbearing potential, and has a high risk for congenital malformations when used just before or during pregnancy.

The EU PPP was evaluated in 2002–3 during a regulatory procedure and because of pregnancies reported throughout Europe. The Pharmacovigilance Working Party (PhVWP) of the Committee of Human Medicinal Products (CHMP) of the European Commission is monitoring the current PPP for isotretinoin on a regular basis. The regulatory authority of the U.K., which is the Reference Member State in Europe for Roaccutane, reported that up to January 2010, 105 risk-exposed pregnancies had been spontaneously reported in the U.K. This was mentioned in a recent publication on the guidelines for isotretinoin use in the U.K.²³ This publication also presents results from an audit performed by the British Association of Dermatologists (BAD) on isotretinoin use and three out of the four audit points concerned the PPP.

Recently, another tretinoin has been approved for the European market, namely alitretinoin for use in the treatment of eczema. This product's PPP will be closely monitored because this product will also be prescribed for a relatively young population including women of childbearing age. Adherence to a strict programme such as iPledge is a burden for all stake-

holders and there is no way of completely avoiding human-related failure.

The isotretinoin PPP has to be evaluated and closely monitored in all countries but also better-designed studies will have to be performed to gain insight into the full picture before taking any new measures. This review of studies in Europe performed so far shows failures in the implementation of this PPP. Therefore, the isotretinoin PPP must be scrutinized to identify whether new measures should be taken or whether the failures in the implementation need to be corrected. New measures should take into account the definition of the ultimate goal of a PPP and the acceptable burden. In the meantime, stakeholders could make a start with adjustments in the implementation of the PPP by taking responsibility and enhancing the performance by explicit instructions, monitoring the performance and adjusting, if necessary.

What's already known about this topic?

- The situation of pregnancies and isotretinoin use in the U.S.A.
- Occurrence of pregnancies despite an isotretinoin pregnancy prevention programme (PPP).
- Compliance with the PPP in the U.S.A.

What does this study add?

- A review of the studies and case reports in Europe.
- An overview of the European situation.
- Identification of compliance issues with the PPP in Europe.

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