EDITORIAL

A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris

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Abstract

Since the introduction of generic oral isotretinoin there have been discussions around harmonizing the summary of product characteristics of each formulation. As a result of these discussions, a European Directive concerned with the prescribing of oral isotretinoin has been introduced and the FDA (Food and Drugs Administration) has recently implemented new regulations. The aims of this article are to summarize the history of the processes involved, outline the new recommendations and discuss the impact of these changes in clinical practice.

Background

Schering Health Care was the first company to introduce a generic version of oral Isotretinoin into the UK market. The UK licence for this generic formulation of isotretinoin was granted on 16 August 2001; however, Schering did not launch the product until February 2002. Soon after this product launch, issues surrounding the licence product information, i.e. the summary of product characteristics (SPC), were raised in the UK. Every licensed product has an SPC that requires approval by the UK Regulatory Authority (MHRA). There are no general requirements for harmonization procedures of generics but a generic application using the Europe Union (EU) mutual recognition procedure frequently triggers a harmonization process if there are any discrepancies across the national SPC for the same substance. As a number of other generic versions of oral isotretinoin were available in other European countries including Germany and France, the product information had to undergo a European Mutual Recognition procedure (MRP). The implicit aim of this was to harmonize product information across Europe so that all new products provided the same summary of product characteristics. This process highlighted inconsistencies between Schering Health Care’s generic isotretinoin in the UK and the information for Roaccutane (Roche’s product) in the UK.

The differences included discrepancies in dosage regimens, the need for an oral contraceptive as well as the need for regular pregnancy testing and blood monitoring.

A consensus on the final version of the SPC was not reached at the European MRP. Hence, the French regulation authorities invoked an arbitration procedure where the French, UK and all Roche SPC were referred to the European Committee on Proprietary Medicinal Products (CPMP). Via this arbitration procedure the product information for isotretinoin was harmonized. This now clarifies indications for use, includes the recommendation for an age limit and advice on dosing. Monitoring of lipids and liver function tests at baseline/pretreatment, at one month into therapy and three monthly thereafter is recommended and advice on when scarring can be treated is given. However, the most significant recommendation agreed at this arbitration was the decision to develop and implement a pregnancy prevention programme (PPP). Table 1 outlines the recommendations and clarifies the current position compared to the situation prior to the harmonization process.
The pregnancy prevention programme

The regulatory authority in each country has had to approve the PPP. This programme embraces issues around education, therapy management and control of distribution of the drug. With respect to education, it suggests that both patients and prescribers must be fully aware of teratogenicity, the patient should acknowledge the problem, supply a consent form, and have detailed counselling by the clinician prior to and during treatment. Therapy management includes medically supervised pregnancy testing before, during and 5 weeks after therapy and in turn includes advice on contraception usage. The distribution control suggests that only 30 days of oral isotretinoin can be supplied at one time and the prescription will only be valid for 7 days from the date of administration. The PPP has had to be approved nationally with the regulatory authority in each country and implementation dates across Europe have varied considerably.

Mandatory pregnancy testing is expected pre-therapy and 5 weeks post-therapy. It has been suggested that the initial test can be done up to 2 weeks prior to the start of treatment providing contraception is used in those who require it. In addition, monthly pregnancy testing is recommended throughout the treatment period. The treatment should ideally start on day 3 of the menstrual cycle. With respect to contraception, the PPP suggests that where possible patients should agree to at least one and preferably two complementary methods of effective contraception including a barrier method before therapy is initiated.

Table 1 Summary of the recommendations

<table>
<thead>
<tr>
<th></th>
<th>Pre-European Directive</th>
<th>Post-European Directive</th>
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<tbody>
<tr>
<td>Dosage recommendations</td>
<td>Between 0.5 mg/kg and 1 mg/kg</td>
<td>Treatment to start at 0.5 mg/kg</td>
</tr>
<tr>
<td>Acne severity</td>
<td>Isotretinoin was previously recommended as first-line therapy for severe acne (nodular, conglobata) as well as acne not responding to at least 3 months of systemic antibiotics combined with topical therapy.</td>
<td>The new recommendations suggest isotretinoin should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy. The inference of this being that it should now not be used at all as first-line therapy.</td>
</tr>
<tr>
<td>Age limit</td>
<td>Previously no age limit</td>
<td>Not recommended in children under 12 years of age</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Liver enzymes and lipids should be checked before treatment and 1 month after the maximum dosage has been used</td>
<td>Check before and 1 month after starting treatment and every 3 months thereafter</td>
</tr>
<tr>
<td>Physical peels and laser</td>
<td>It was recommended that chemical and physical peeling should be avoided during treatment and for 6 months afterwards and that wax depilation should be avoided during and 6 weeks post-therapy.</td>
<td>All forms of peeling and wax depilation should be avoided during therapy and 6 months afterwards.</td>
</tr>
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</table>

The dispensing restrictions are not applicable to males. The dispensing process is aimed at ensuring that females do not get extended periods of treatment without having pregnancy tests performed. As suggested previously, female patients will be given a 30-day supply and their prescription will only be valid for 7 days from the date of administration. The PPP has had to be approved nationally with the regulatory authority in each country and implementation dates across Europe have varied considerably.

Aims of the European Directive

The aims of the directive are to ensure generic prescribing is harmonized and delivered appropriately throughout the EU in an attempt to minimize the risk of adverse effects including pregnancy.

Impact of the European Directive in clinical practice

This programme, which advocates changes in prescribing, is going to produce practical, financial and clinical difficulties. Time constraints for healthcare professionals are inevitable, as they will be seeing patients more frequently.

Practical problems

There are potentially going to be some problems implementing this harmonized approach. Female patients are going to have to attend more frequently and this is not always going to be possible due to the nature of this young mobile population. The European Directive on isotretinoin prescribing does not appear to recognize the careful prescribing habits of dermatologists and some general practitioners, which is currently in place as
reflected in the low incidences of unwanted adverse effects and teratogenic effects reported in Europe.

The PPP has suggested that responsibility for the assessment of pregnancy tests and the administration of further prescriptions lies with the clinician. Although nurse-led clinics, which have been implemented in some areas of the UK, may help to some degree, it is still going to be necessary for clinical and prescribing input from experienced physicians. The increase in number of prescriptions is going to impact on the pharmacy departments.

Financial problems
This directive will lead to an increased financial burden for the different healthcare services in the EU due to the extra visits, investigations and prescriptions required. The recommendations have no evidence-based background.

Clinical problems
Clinical problems relating to the implementation of this approach include difficulties if females have irregular menses, potential lack of continuity of treatment due to unavailability of patient and/or healthcare workers as well as forgotten tests. These factors may all contribute to early cessation and/or partial treatment resulting in ineffective medical management, and hence waste of valuable resources. Given potential side-effects of oral contraceptives, it may not always be appropriate to insist on all patients regardless of pregnancy risk using specific contraceptives. The relative risk of venous thromboembolic events are summarized in Table 2.\(^1\)

In addition, the recommendations suggest that isotretinoin should no longer be used as first-line therapy and/or should not be used below the age of 12 years. Experienced dermatologists who have been treating severe forms of acne and using isotretinoin for more than 20 years raise the question of whether this poses a significant ethical problem as delaying treatment may result in significant clinical and psychological scarring. There are many publications advocating the use of isotretinoin for severe acne and scarring acne in the literature\(^2\); hence delaying this effective therapy in those cases may go against best and evidence-based practice. This could result in litigation particularly if scarring results from the delay. The recommendations to start at 0.5 mg/kg/day and to titrate the dose as tolerated are well received when using isotretinoin for conventional acne. However, some patients with persistent acne, especially in the mature age group, as well as cases where side-effects are not tolerated at these recommended doses will require low dose and possibly intermittent treatment. This has been advocated for some of these specific cases in the literature.\(^1\) The recommended PPP and monitoring will have significant impact in terms of time, costs and thromboembolic risk if adopted as part of the routine management of some patients.

Other cultural and social issues might impact on implementation as not all fertile females will wish to take oral contraceptives. In addition, the control of distribution of drugs suggest that females will only be allowed 30 days whereas males can have longer prescriptions. This may lead to some issues around discrimination.

FDA regulations
The USA have adopted a more rigid programme to pregnancy prevention and monitoring. On 12 August 2005 the Food and Drug Administration (FDA) announced that both male and female users of ‘Accutane’ (oral isotretinoin) would have to enrol into the National Registry ‘iPLEDGE’ by 31 December 2005. If this is not achieved, patients will no longer be able to receive the drug in the USA. Women of childbearing age have to provide two negative pregnancy tests before their initial prescription, show proof of another negative pregnancy test before each monthly repeat prescription, and use two forms of contraception throughout therapy and for 30 days after treatment. They need to enter these forms of contraception into the registry. All patients sign a document confirming that they are aware of potential adverse effects of isotretinoin including depression and suicidal thoughts. Prescribing clinicians and dispensing pharmacists also have to sign up to this registry.

Conclusions
The European Directive aims to ensure that systemic isotretinoin prescribing is harmonized, which seems sensible. The aim to minimize the risk of pregnancy in patients prescribed oral isotretinoin is something all clinicians would support. However, the approach that has been advocated by the European Directive and recent recommendations being enforced by the FDA will pose some very difficult practical, economic and ethical issues for prescribing clinicians, patients and other healthcare workers. The pharmaceutical industry is bound by the EU

### Table 2 Relative risks of venous thromboembolic episodes

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<tr>
<th>Risk (per 100 000)</th>
<th>Risk (cases per 100 000)</th>
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<tr>
<td>Non-oral contraceptive user</td>
<td>5–10</td>
</tr>
<tr>
<td>Oral contraceptive users (&lt; 50 mg ethinyloestradiol)</td>
<td>10–15</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^1\) The recommended PPP and monitoring will have significant impact in terms of time, costs and thromboembolic risk if adopted as part of the routine management of some patients.

\(^2\) The FDA regulations
and national pharmaceutical legislation. The SPC and PPP represent the approved information on how best to use the product safely and effectively. In EU countries, clinicians are free to prescribe according to their professional judgement. However, in the event of any medical problems, failure to follow recommended prescribing could result in liability.

One unfortunate consequence of this strict regimen may be a reduction in the usage of isotretinoin, which could potentially disadvantage patients who require this effective treatment. In addition, the restriction of isotretinoin as a second-line therapy may have consequences on the course of acne, the evolution of acne scaring, and on the quality of life in many acne patients.

Declaration

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References