EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2011
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Patient Health Protection

Assessment Report pursuant to Article 29(4) of Directive 2001/83/EC, as amended

Isotretinoin and associated names

INN of the active substance: isotretinoin

Marketing authorisation holder: Ranbaxy (UK) Limited

Procedure no: EMEA/H/A-29/1276

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

1.1. Mutual recognition procedure (MRP) and CMD(h) 60 day procedure

The marketing authorisation holder (MAH) Ranbaxy (UK) Limited submitted an application for mutual recognition of isotretinoin and associated names, 10 and 20 mg soft capsules on the basis of the marketing authorisation granted by the United Kingdom on 20 November 2006.

The application was submitted to the concerned Member States (CMS): France and Spain.

The mutual recognition procedure UK/H/1063/01-02/MR started on 24 February 2010.

On day 90, major issues on bioequivalence, raised by Spain, remained unsolved; hence the procedure was referred to CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by United Kingdom on 25 May 2010. The CMD(h) 60 day procedure was initiated on 31 May 2010. Day 60 of the CMD(h) procedure was on 29 July 2010, and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by the United Kingdom on 29 July 2010 Spain raised public health objections concerning the demonstration of bioequivalence of isotretinoin to the originator.

2. Scientific discussion during the referral procedure

2.1. Introduction

Isotretinoin is a vitamin A derivative indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. Isotretinoin is effective against severe acne via a direct effect on the size and activity of sebaceous glands, plus a probable dermal anti-inflammatory effect.

Isotretinoin Ranbaxy 10 mg & 20 mg, capsules (soft) was authorised in the reference member state (UK) under Article 10 of Directive 2001/83/EC, and the application was submitted in the concerned member states (France and Spain) under the mutual recognition procedure.

At the time of the initial authorisation, the UK considered that bioequivalence study under fasting conditions was satisfactory for all oral immediate release products as the fasted state was considered to be most discriminating between formulations and the bioequivalence guideline was not clear on requirements for bioequivalence for products where the summary of product characteristics (SPC) advises administration with food.

However, in the mutual recognition application the MAH proposed SPC indicated that the capsules should be taken with food once or twice daily. Considering that the MAH had performed only one bioequivalence study, under fasting conditions (study 237/00[1]) objections were raised to the approval of these marketing authorisations. Disagreement remained as demonstration of bioequivalence in fed conditions was considered necessary for this product according to the current guidance on investigation of bioequivalence. The procedure was therefore referred to the CHMP and a list of questions was adopted, in particular:

The applicant is requested to justify that their Isotretinoin 10mg and 20mg capsules are bioequivalent to the reference product under normal conditions of use as specified in the SPC i.e. in the fed state.

[1] Study 237/00 was an open label, balanced, randomised, two treatment, two period, two sequence, single dose, crossover bioequivalence study on Isotretinoin formulations comparing Isotretinoin 20mg capsules from the MAH (Ranbaxy) with the originator's 20mg capsules (Roaccutane from Roche) under fasting conditions in healthy adult human male subjects.

2.2. Critical evaluation

The MAH provided a summary report of a bioequivalence study (122_ISOTR_10[2]). Subjects enrolled were 18-45 years of age, had body mass index (BMI) ≥18.5 and <30.0 kg/m^2 and haemoglobin level ≥13,0 g/dl. All subjects enrolled received standard meals – breakfast, lunch, snacks, dinner, as appropriate - and were fasted overnight for at least 10 hours. No food was allowed for at least 4h after the dose administration.

Sixty four (64) subjects were to be enrolled into the study, however 60 were enrolled. Fifty six (56) subjects completed both study periods. One subject was withdrawn and 3 dropped out of the study. Pharmacokinetic and statistical analysis were therefore performed on data from 56 subjects. Results are shown in the table below.

Pharmacokinetic Parameter	Isotretinoin	4-oxo-isotretinoin
ln C_{max}	87.42% (76.27% - 100.21%)	82.86%
ln AUC_{0-t}	85.36% (76.06% - 95.79%)	85.01%
ln $AUC_{0-\infty}$	88.58% (79.73% - 98.41%)	85.81%

For isotretinoin and its metabolite 4-oxo-isotretinoin, the ratio of test and reference product averages (lean square means) for the pharmacokinetic parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within 80-125%. However, statistical analysis showed that the 90% confidence intervals for the above mentioned pharmacokinetic parameters were outside the regulatory acceptance limits of 80-125%.

Therefore, this study has failed to show that the test product (Isotretinoin soft gelatin capsules 20mg from Ranbaxy Laboratories Limited, India) and the reference product (ROACCUTANE 20mg soft capsules from Roche Products Limited, UK) are bioequivalent under fed conditions.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

The MAH developed a formulation of Isotretinoin soft gelatin capsules and conducted a bioequivalence study (No 237/00) demonstrating the similarity of the generic with the innovator product in healthy, adult, human male subjects under fasting conditions. This formed the basis for the approval in the reference member state and was in line with guidance at the time.

During the mutual recognition procedure demonstration of bioequivalence in fed state was considered essential and the matter was referred to the CHMP. The absorption of Isotretinoin in fed state is larger than that observed in fasted state[3], and this motivates the SPC recommendation of intake with food (section 4.2 Posology). The CHMP agreed that a study in the fed state was essential and in line with the current recommendations in the current guidance on the investigation of bioequivalence.

The results of study 122_ISOTR_10 in healthy adult human male subjects have failed to show that the Isotretinoin Ranbaxy generic is bioequivalent to the originator product in real conditions of use (fed conditions), as the 90% CI fell outside the 80-125% interval, which constitutes a risk to public health.

The totality of data submitted does not support the conclusion that the product is bioequivalent. It is therefore considered that the particulars submitted in support of the application do not comply with

[2] Study 122_ISOTR_10 was an open label, balanced, randomised, two treatment, two period, two sequence, single dose, crossover bioequivalence study comparing Isotretinoin 20mg capsules from the MAH (Ranbaxy) with the originator's 20mg capsules (Roaccutane from Roche) under fed condition in healthy adult human male subjects.

[3] *Colburn WA et al* (1983) *Food increases the bioavailability of Isotretinoin*. J Clin Pharmacol 23(11-12): 534-9.

article 10 of Directive 2001/83/EC as amended. The Committee further considered that it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product and, in these circumstances, the marketing of the products constitutes a risk to public health.

The CHMP noted that the provision of a new bioequivalence study in the fed state using the current formulation may not be accepted as replacing the existing failed study. A large highly powered bioequivalence study showing test/reference ratios for AUC and C_{max} within the 80-125% range, with tight confidence intervals lying entirely within the confidence intervals for the existing study, could in principle establish bioequivalence. It is likely that re-formulation of the product will be necessary and a new study then conducted.

2.5. Conclusions and benefit risk assessment

The CHMP considered that the data submitted in support of this application failed to show bioequivalence between the test and the reference product, and that therefore the product is not approvable for the sought indications.

Based on:

- the results of the bioequivalence study in fed conditions provided by the MAH,
- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the particulars submitted in support of the application do not comply with article 10 of Directive 2001/83/EC as amended. The Committee further considered that it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product and that, in these circumstances, the marketing of the product constitutes a risk to public health.

Therefore, the Committee adopted an opinion recommending the refusal of the marketing authorisations in the concerned member states and the suspension of the marketing authorisations in the reference member state, subject to the conditions outlined in annex III of the Opinion.