

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT(S), MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Austria		Nycomed Pharma GmbH, EUROPLAZA Gebäude F Technologiestraße 5 A-1120 Wien	Alvesco 40 Mikrogramm Dosieraerosol	40 µg	Pressurised inhalation, solution	Inhalation use
Austria		Nycomed Pharma GmbH, EUROPLAZA Gebäude F Technologiestraße 5 A-1120 Wien	Alvesco 80 Mikrogramm Dosieraerosol	80 µg	Pressurised inhalation, solution	Inhalation use
Austria		Nycomed Pharma GmbH, EUROPLAZA Gebäude F Technologiestraße 5 A-1120 Wien	Alvesco 160 Mikrogramm Dosieraerosol	160 µg	Pressurised inhalation, solution	Inhalation use
Austria		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Amavio 40 Mikrogramm Dosieraerosol	40 µg	Pressurised inhalation, solution	Inhalation use
Austria		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Amavio 80 Mikrogramm Dosieraerosol	80 µg	Pressurised inhalation, solution	Inhalation use
Austria		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Amavio 160 Mikrogramm Dosieraerosol	160 µg	Pressurised inhalation, solution	Inhalation use
Belgium	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-1080 Brussels		Alvesco 40 microgram, aërosol, oplossing	40 µg	Pressurised inhalation, solution	Inhalation use
Belgium	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-1080 Brussels		Alvesco 80 microgram, aërosol, oplossing	80 µg	Pressurised inhalation, solution	Inhalation use

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Belgium	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-1080 Brussels		Alvesco 160 microgram, aërosol, oplossing	160 µg	Pressurised inhalation, solution	Inhalation use
Bulgaria		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 Inhaler	40 µg	Pressurised inhalation, solution	Inhalation use
Bulgaria		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use
Bulgaria		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use
Cyprus		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 micrograms Inhaler	40 µg	Pressurised inhalation, solution	Inhalation use
Cyprus		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 micrograms Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use
Cyprus		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 micrograms Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use
Czech Republic	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use
Czech Republic	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Denmark	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 micrograms pressurised inhalation, solution	40 µg	Pressurised inhalation, solution	Inhalation use
Denmark	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 micrograms pressurised inhalation, solution	80 µg	Pressurised inhalation, solution	Inhalation use
Denmark	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 micrograms pressurised inhalation, solution	160 µg	Pressurised inhalation, solution	Inhalation use
Estonia	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 micrograms pressurised inhalation, solution	40 µg	Pressurised inhalation, solution	Inhalation use
Estonia	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 micrograms pressurised inhalation, solution	80 µg	Pressurised inhalation, solution	Inhalation use
Estonia	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 micrograms pressurised inhalation, solution	160 µg	Pressurised inhalation, solution	Inhalation use
Finland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 micrograms pressurised inhalation, solution	40 µg	Pressurised inhalation, solution	Inhalation use

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Finland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 micrograms pressurised inhalation, solution	80 µg	Pressurised inhalation, solution	Inhalation use
Finland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 micrograms pressurised inhalation, solution	160 µg	Pressurised inhalation, solution	Inhalation use
France		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 microgrammes, dose solution pour inhalation en flacon pressurisé	40 µg	Pressurised inhalation, solution	Inhalation use
France		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 microgrammes, dose solution pour inhalation en flacon pressurisé	80 µg	Pressurised inhalation, solution	Inhalation use
France		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 microgrammes, dose solution pour inhalation en flacon pressurisé	160 µg	Pressurised inhalation, solution	Inhalation use
Germany	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 Mikrogramm Druckgasinhalation, Lösung	40 µg	Pressurised inhalation, solution	Inhalation use
Germany	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Mikrogramm Druckgasinhalation, Lösung	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Germany	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Mikrogramm Druckgasinhalation, Lösung	160 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Alvesco 80 mcg/Dose	80 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Alvesco 160 mcg/Dose	160 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Freathe 80 mcg/Dose	80 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Freathe 160 mcg/Dose	160 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Amavio 80 mcg/Dose	80 µg	Pressurised inhalation, solution	Inhalation use
Greece	Nycomed Hellas S.A. Kifissias Ave 196 GR-15231 Chalandri		Amavio 160 mcg/Dose	160 µg	Pressurised inhalation, solution	Inhalation use
Hungary	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 mikrogramm túlnyomásos inhalációs oldat	40 µg	Pressurised inhalation, solution	Inhalation use
Hungary	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 mikrogramm túlnyomásos inhalációs oldat	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Hungary	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 mikrogramm túlnyomásos inhalációs oldat	160 µg	Pressurised inhalation, solution	Inhalation use
Iceland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 innúdalyf	40 µg	Pressurised inhalation, solution	Inhalation use
Iceland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 innúdalyf	80 µg	Pressurised inhalation, solution	Inhalation use
Iceland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 innúdalyf	160 µg	Pressurised inhalation, solution	Inhalation use
Ireland	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz Germany		Alvesco 40 micrograms pressurised inhalation solution	40 µg	Pressurised inhalation, solution	Inhalation use
Ireland	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz Germany		Alvesco 80 micrograms pressurised inhalation solution	80 µg	Pressurised inhalation, solution	Inhalation use
Ireland	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz Germany		Alvesco 160 micrograms pressurised inhalation solution	160 µg	Pressurised inhalation, solution	Inhalation use
Italy		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco	40 µg	Pressurised inhalation, solution	Inhalation use
Italy		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco	80 µg	Pressurised inhalation, solution	Inhalation use

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Italy		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco	160 µg	Pressurised inhalation, solution	Inhalation use
Latvia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 inhalators	40 µg	Pressurised inhalation, solution	Inhalation use
Latvia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 inhalators	80 µg	Pressurised inhalation, solution	Inhalation use
Latvia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 inhalators	160 µg	Pressurised inhalation, solution	Inhalation use
Lithuania	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	40 µg	Pressurised inhalation, solution	Inhalation use
Lithuania	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	80 µg	Pressurised inhalation, solution	Inhalation use
Lithuania	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	160 µg	Pressurised inhalation, solution	Inhalation use
Luxembourg	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-B-1080 Brussels		Alvesco 40 Aérosol doseur	40 µg	Pressurised inhalation, solution	Inhalation use
Luxembourg	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-B-1080 Brussels		Alvesco 80 Aérosol doseur	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Luxembourg	Nycomed Belgium s.c.a./c.v.a. Gentsesteenweg 615 B-B- 1080 Brussels		Alvesco 160 Aérosol doseur	160 µg	Pressurised inhalation, solution	Inhalation use
Malta		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 Inhaler	40 µg	Pressurised inhalation, solution	Inhalation use
Malta		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use
Malta		Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use
Netherlands	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 Inhalator	40 µg	Pressurised inhalation, solution	Inhalation use
Netherlands	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Inhalator	80 µg	Pressurised inhalation, solution	Inhalation use
Netherlands	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Inhalator	160 µg	Pressurised inhalation, solution	Inhalation use
Norway	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 micrograms/dose inhalasjonsaerosol, oppløsning	40 µg	Pressurised inhalation, solution	Inhalation use
Norway	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 micrograms/dose inhalasjonsaerosol, oppløsning	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Norway	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 micrograms/dose inhalasjonsaerosol, oppløsning	160 µg	Pressurised inhalation, Solution	Inhalation use
Poland	Nycomed Pharma Sp. z o.o. Al. Jerozolimskie 146 A PL-02-305 Warszawa		Alvesco 40	40 µg	Pressurised inhalation, solution	Inhalation use
Poland	Nycomed Pharma Sp. z o.o. Al. Jerozolimskie 146 A PL-02-305 Warszawa		Alvesco 80	80 µg	Pressurised inhalation, solution	Inhalation use
Poland	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160	160 µg	Pressurised inhalation, solution	Inhalation use
Portugal		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 Inalador	40 µg	Pressurised inhalation, solution	Inhalation use
Portugal		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 Inalador	80 µg	Pressurised inhalation, solution	Inhalation use
Portugal		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 Inalador	160 µg	Pressurised inhalation, solution	Inhalation use
Romania	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 Inhaler	40 µg	Pressurised inhalation, solution	Inhalation use
Romania	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Romania	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use
Slovak Republic	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 Inhalátor	40 µg	Pressurised inhalation, solution	Inhalation use
Slovak Republic	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Inhalátor	80 µg	Pressurised inhalation, solution	Inhalation use
Slovak Republic	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Inhalátor	160 µg	Pressurised inhalation, solution	Inhalation use
Slovenia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 µg inhalacijska raztopina pod tlakom	40 µg	Pressurised inhalation, solution	Inhalation use
Slovenia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 µg inhalacijska raztopina pod tlakom	80 µg	Pressurised inhalation, solution	Inhalation use
Slovenia	ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 µg inhalacijska raztopina pod tlakom	160 µg	Pressurised inhalation, solution	Inhalation use
Spain		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 40 mcg solución para inhalación en envase a presión	40 µg	Pressurised inhalation, solution	Inhalation use
Spain		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 80 mcg solución para inhalación en envase a presión	80 µg	Pressurised inhalation, solution	Inhalation use

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Spain		ALTANA Pharma AG Byk-Gulden-Str. 2 D-78467 Konstanz	Alvesco 160 mcg solución para inhalación en envase a presión	160 µg	Pressurised inhalation, solution	Inhalation use
Sweden	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	40 µg/dose	Pressurised inhalation, solution	Inhalation use
Sweden	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	80 µg/dose	Pressurised inhalation, solution	Inhalation use
Sweden	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco	160 µg/dose	Pressurised inhalation, solution	Inhalation use
United Kingdom	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 40 Inhaler	40 µg	Pressurised inhalation, solution	Inhalation use
United Kingdom	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 80 Inhaler	80 µg	Pressurised inhalation, solution	Inhalation use
United Kingdom	Nycomed GmbH Byk-Gulden-Str. 2 D-78467 Konstanz		Alvesco 160 Inhaler	160 µg	Pressurised inhalation, solution	Inhalation use

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE
SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE
LEAFLET PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ALVESCO AND ASSOCIATED NAMES (see Annex I)

Ciclesonide is a glucocorticoid used to treat obstructive airway disease. Alvesco 40 Inhaler, 80 Inhaler and 160 Inhaler are products containing ciclesonide, delivered in a pressurized metered dose inhaler containing ethanolic hydrofluoroalkane-134A as propellant. The inhaler is an aluminium canister containing 120 doses of either 40 µg, 80 µg or 160 µg ex actuator, corresponding to 50, 100, or 200 µg per puff ex valve. This product was submitted under article 10.3 of the Directive 2001/83/EC.

During the mutual recognition procedure, the regulatory authorities of France were of the opinion that the product raised a potential serious risk to public health on safety and efficacy grounds.

The following issues were raised concerning this application:

1. The risk/benefit analysis of the use of higher doses of ciclesonide in the treatment of severe asthmatics, as the supportive data, interpreted according to the CHMP guidelines, do not allow authorization of regular daily doses in excess of 160 micrograms in the intended populations.

The CHMP referred to the NfG on the Clinical Investigation of Medicinal Products in the Treatment of Asthma CPMP/EWP/2922/01, and was of the opinion that the MAH had not adequately justified the inclusion of the 320µg/d and 640µg/d ciclesonide. The data presented in the responses only reiterated the fact that there is no effective dose ranging data comparing 160, 320 and 640µg/d. Additionally, no study submitted by the MAH showed a significant improvement in FEV1 above 160µg/d in asthmatics.

2. The scientific rationale for difference of opinion regarding the proposed SPC Type II variations' wording of ciclesonides' dose effectiveness on reducing the frequency of exacerbations in severe asthma as drafted in Sections 4.2 and 5.1 by the RMS on the 19th October 2007 following the CMDh hearing.

The CHMP considered the MAH's response to support the additional changes to Section 4.2 of the SPC. Study MI-129 did not define an adequate primary endpoint in accordance with the current guidelines for asthma. The CHMP was concerned with the MAH's continued reliance on the results of study MI-140 and its recognized insufficiencies: a short term study of 3 months instead of a minimum of 6 months; the lack of a 320µg/d arm; and the debatable value of improvement in severe exacerbations at the higher 640 dose with no further improvement in lung function. In addition the CHMP was concerned with introducing the notion of switching from moderate to high dose inhaled corticosteroids to higher doses of Alvesco, as this was not in the original submission. As a conclusion to the evaluation, the CHMP was of the opinion that the proposed wording for Section 4.2 at the end of CMDh would continue to be adequate with the following amendment:

The recommended dose of Alvesco is 160 micrograms once daily, which leads to asthma control in the majority of patients. However in severe asthmatics, a 12 week study has shown that a dose of 640µg/d (given 320µg/d twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function (see section 5.1).

Additionally, the MAH agreed to amend the wording for Section 5.1 in order to include more detail on Study M1 140, to indicate that there was a statistically significant difference between the doses of 160 micrograms/day and 640 micrograms/day ciclesonide with regards to the occurrence of an exacerbation after the first day of the study. The proposed wording of the Package Leaflet at the end of the CMDh was also modified to be in line with the amendments to the SPC. The Package Leaflet amendments include a note on increasing the dosage of Alvesco up to 640 micrograms/day, delivered as 320 micrograms twice daily, for a short period in patients who experience a worsening of their

asthma symptoms. However, this note also refers to the lack of data available to confirm that this approach has additional therapeutic effects after 3 months with the highest dose available.

3. The MAH was asked to explain the different feasible scientific approaches for conducting a well designed study comparing 160 µg, 320 µg and 640 µg in order to clarify the efficacy/safety ratio of 160 µg compared to 320 µg and 640 µg in severe asthmatics. Such a study must comply with the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma CPMP/EWP/2922/01.

The CHMP was of the opinion that the MAH had identified a feasible target patient population in the response. These patients are partially controlled as per the latest GINA guidelines. The treatment period and primary endpoint appear adequate to measure the potential benefit of higher doses of ciclesonide. A study powered to show a statistically significant difference between all doses, is considered to be the most adequate from a statistical and clinical point of view. The trial proposed (referred to as Scenario B) should generate all the information needed by the applicant in order to submit a variation to Section 4.2 of the SPC which would include a recommendation to use higher doses of ciclesonide as proposed by the MAH.

GROUNDINGS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas:

- The proposed wording for Section 4.2 of the SPC at the end of CMDh procedure has been amended to reflect that in severe asthmatics, a 12 week study has shown that a dose of 640µg/d (given 320µg/d twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function.
- The proposed wording for Section 5.1 of the SPC at the end of the CMDh procedure has been amended to include more detail on Study M1 140.
- The proposed wording for Sections 3, 4 and 5 of the Package Leaflet at the end of the CMDh procedure have been amended accordingly.
- The MAH has proposed an adequate study which would resolve the outstanding question on the long term use of 320 µg and 640 µg daily.

the CHMP has recommended the granting of the Marketing Authorisation(s) for Alvesco and associated names, with amendments to the relevant sections of the Product Information and with commitments to be fulfilled. The revised Summary of Product Characteristics, labelling and package leaflet are set out in Annex III of the Opinion for Alvesco and associated names (see Annex I). The conditions for the Marketing Authorisation are set out in Annex IV.

The applicant/MAH is requested to commit to obtaining scientific advice in relation to exploring a suitable study design, and execute such study (ies) to provide further information on the use of the higher dose of Alvesco in the control of severe asthma.

ANNEX III

**AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING
AND PACKAGE LEAFLET**

**AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY
OF PRODUCT CHARACTERISTICS**

The valid Summary of Product Characteristics is the final version achieved during the Coordination group procedure with the following amendments:

4.2 Posology and method of administration

The medicinal product is for inhalation use only.

Dosing recommendation for adults and adolescents:

The recommended dose of Alvesco is 160 micrograms once daily, which leads to asthma control in the majority of patients. However in severe asthmatics, a 12 week study has shown that a dose of 640 micrograms/day (given 320 micrograms twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function (see section 5.1).

5.1 Pharmacodynamic properties

Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, ciclesonide is enzymatically converted in the lungs to the principal metabolite (C21-des-methylpropionyl-ciclesonide) which has a pronounced anti-inflammatory activity and is thus considered as the active metabolite.

In four clinical trials, ciclesonide has been shown to reduce airway hyperresponsiveness to adenosine monophosphate in hyperreactive patients with maximal effect observed at the dose of 640 micrograms. In another trial, pretreatment with ciclesonide for seven days significantly attenuated the early and late phase reactions following inhaled allergen challenge. Inhaled ciclesonide treatment was also shown to attenuate the increase in inflammatory cells (total eosinophils) and inflammatory mediators in induced sputum.

A controlled study compared 24-hour plasma cortisol AUC in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, treatment with ciclesonide 320, 640, and 1280 micrograms/day did not statistically significantly lower the 24-hour time averages of plasma cortisol (AUC(0-24)/24 hours) nor was a dose-dependent effect seen.

In a clinical trial involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 320 micrograms or 640 micrograms/day over 12 weeks. After stimulation with 1 and 250 micrograms cosyntropin, no significant changes in plasma cortisol levels were observed versus placebo.

Double-blind placebo-controlled trials of 12-weeks duration in adults and adolescents have shown that treatment with ciclesonide resulted in improved lung function as measured by FEV1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled beta-2 agonist.

In a 12-week study of 680 severe asthmatics, previously treated with 500 - 1000 micrograms fluticasone propionate per day or equivalent, 87.3% and 93.3% of patients remained exacerbation-free during treatment with 160 or 640 micrograms of ciclesonide, respectively. At the end of the 12 week study period, the results showed a statistically significant difference between the doses of 160 micrograms and 640 micrograms/day ciclesonide with regard to the occurrence of an exacerbation after the first day of the study: 43 patients/339 (= 12.7%) in the 160 micrograms/day group and 23 patients/341 (6.7%) in the 640 micrograms/day group (Hazard ratio=0.526; p= 0.0134). Both ciclesonide doses resulted in comparable FEV1 values at 12 weeks. Treatment-related adverse events were seen in 3.8% and 5% of patients treated with 160 or 640 micrograms per day of ciclesonide respectively. No study was performed to compare 160 micrograms, 320 micrograms and 640 micrograms daily dose in patients with severe asthma.

**AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE
LABELLING**

The valid labelling is the final version achieved during the Coordination group procedure.

**AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE
LEAFLET**

The valid package leaflet is the final version achieved during the Coordination group procedure with the following amendments:

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alvesco 40, 80 and 160 micrograms pressurised inhalation, solution Ciclesonide

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet the information is arranged as follows:

1. What Alvesco is and what it is used for
2. Before you use Alvesco (This section contains important information for your safety)
3. How to use Alvesco
4. Possible side effects
5. How to store Alvesco
6. Further information

3. HOW TO USE ALVESCO

Always use this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- If you have just started to use this medicine instead of, or as well as, taking corticosteroid tablets, see section 2, Patients who are already taking corticosteroid tablets.

How much Alvesco should I take each day?

Your doctor will have spoken to you about how much of your medicine you need to take each day. This will depend on your individual need.

- The recommended dose of Alvesco is 160_micrograms once daily, which leads to asthma control in the majority of patients.
- In some patients a dose reduction to 80_micrograms, once daily, may be an adequate dose for maintaining effective control of their asthma.
- An increased dosage of Alvesco may become necessary for a short period of time in patients who suffer a severe worsening of their asthma symptoms. This can be up to 640 micrograms per day, delivered as 320 micrograms twice daily but no data confirming the additional therapeutic effect after 3 months with these higher doses are available.

If necessary, your doctor may also prescribe corticosteroid tablets and/or, in the case of an infection, an antibiotic.

- Your doctor will adjust your dose to the minimum necessary to control your asthma.

- You should start to notice an improvement in your symptoms (wheezing, tight chest and coughing) within 24 hours.

When should I use my Alvesco inhaler?

In most cases, either in the morning or in the evening – as one or two puffs once a day. Follow your doctor's instructions very carefully. It is important that you take Alvesco regularly every day, even if you feel better.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alvesco can cause side effects, although not everybody gets them.

The side effects seen with Alvesco are usually mild. In most cases you can continue with your treatment. The side effects you may experience are:

Very rare side effects (fewer than 1 of 10,000 patients treated):

Immediate or delayed hypersensitivity reactions such as swelling of lips, tongue and throat (angioedema). Patients experiencing these symptoms should stop using the medicine and seek immediate medical attention.

Uncommon side effects (fewer than 1 in every 100 patients treated):

- hoarseness, cough after inhalation, increase in wheezing after inhalation
- bad taste, burning, inflammation, irritation, dryness of mouth or throat
- skin rash and/or eczema causing itching and redness.

Alvesco may affect the normal production of corticosteroids in your body. This is usually seen in patients taking high doses over a long period of time. These rare side effects may include:

- reduced rate of growth in adolescents
- a thinning of the bones
- possible clouding of the lens of the eye (cataracts) causing blurred vision
- loss of vision caused by abnormally high pressure in the eye (glaucoma)
- moon-shaped face, weight gain in the upper body and thinning arms and legs (Cushingoid features or Cushing syndrome).

Adolescents who are receiving treatment for a long period of time should have their height checked regularly by their doctor. If growth rate is slowed, your doctor will adjust your treatment if possible to the lowest dose at which effective control of asthma is maintained.

Corticosteroid tablets can lead to more side effects than a corticosteroid inhaler such as Alvesco. If you have been taking steroid tablets before or during the use of Alvesco, the risk of side effects from the tablets may continue for a period of time. Regular check-ups with your doctor will ensure that you are taking the right dose of Alvesco for you. Regular check-ups will also identify any side effects early on and reduce the chances of them worsening.

Please remember:

The expected benefits of your medicine will usually be greater than the risks of suffering any harmful side effects.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ALVESCO

Keep out of the reach and sight of children.

The container contains a pressurised liquid. Do not store above 50°C.

The container should not be punctured, broken or burned even if it seems empty.

As with most inhaled medicines in pressurised containers, the healing effect of this medicinal product may become smaller when the container is cold. However, Alvesco delivers the same level of dose from minus 10°C to plus 40°C.

Do not use your inhaler after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month.

If your doctor decides to stop treatment or if the inhaler is empty, return it to your pharmacist for safe disposal. This is important as traces of medicine could remain in the container even if you have the impression that it might be empty.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION(S)

CONDITIONS CONSIDERED ESSENTIAL FOR THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT INCLUDING PHARMACOVIGILANCE

The National Competent Authorities, coordinated by the Reference Member State shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holder:

- The applicant/MAH is requested to commit to obtaining scientific advice in relation to exploring a suitable study design, and execute such study (ies) to provide further information on the use of the higher dose of Alvesco in the control of severe asthma.