ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 1220 Wien Austria	Singulair 4 mg – Kautabletten für Kleinkinder	4 mg	Chewable tablets	Oral use	4 mg
Belgium	Merck Sherp & Dohme Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Bulgaria	Merck Sharp and Dohme Bulgaria EOOD 55, Nikola Vaptzarov blvd. EXPO 2000, east wing, sectors B1&B2, 1st fl. 1407 Sofia Bulgaria	Singulair	4 mg	Granules	Oral	
Bulgaria	Merck Sharp and Dohme Bulgaria EOOD 55,Nikola Vaptzarov blvd. EXPO 2000, east wing, sectors B1 & B2, 1st fl. 1407 Sofia Bulgaria	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Cyprus	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	SINGULAIR	4 mg	Granules	Oral	

Member State	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Cyprus	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	SINGULAIR PAEDIATRIC	4 mg	Chewable tablets	Oral use	4 mg
Czech Republic	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	SINGULAIR 4 Mini	4 mg	Chewable tablets	Oral use	4 mg
Denmark	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Singulair Mini 4mg	4mg	Granules	Oral	
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Singulair 4mg	4mg	Chewable tablets	Oral use	4 mg
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.BOX 581 2031 BN Haarlem The Netherlands	Singulair	4 mg	Granules	Oral	
Finland	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem, The Netherlands	Singulair	4 mg	Chewable tablets	Oral use	4 mg

Member State	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Germany	Dieckmann Arzneimittel GmbH, Lindenplatz 1 85540 Haar Germany	Singulair mini 4 mg Granulat	4 mg	Granules	Oral	
Germany	Dieckmann Arzneimittel GmbH, Lindenplatz 1 85540 Haar Germany	SINGULAIR mini 4 mg Kautabletten	4 mg	Chewable tablets	Oral use	4 mg
Greece	VIANEX A.E. Tatoiou Street, Nea Erythrea, 146 71, Greece	Singulair	4 mg	Granules	Oral	
Greece	VIANEX A.E. Tatoiou Street, Nea Erythrea, 146 71, Greece	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Hungary	MSD Magyarország Kft. 1123 Budapest, Alkotás u. 50., Hungary	Singulair	4mg	Chewable tablets	Oral use	4 mg
Iceland	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Granules	Oral	
Iceland	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Ireland	Merck Sharp & Dohme Ltd ; Hertford Road, Hoddesdon, Hertfordshire EN119BU, United Kingdom	Singulair Paediatric	4mg	Granules	Oral	

Member State	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Ireland	Merck Sharp & Dohme Ltd ; Hertford Road, Hoddesdon, Hertfordshire EN119BU United Kingdom	Singulair Paediatric	4 mg	Chewable Tablets	Oral use	4 mg
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Roma Italy	SINGULAIR	4 mg	Granules	Oral	
Italy	Istituto Gentili S.p.A Via B. Croce, 37 56125 Pisa Italy	MONTEGEN	4 mg	Granules	Oral	
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Roma Italy	SINGULAIR	4 mg	Chewable tablets	Oral use	4 mg
Italy	Istituto Gentili S.p.A Via B. Croce, 37 56125 Pisa Italy	MONTEGEN	4 mg	Chewable tablets	Oral	4 mg
Latvia	SIA « Merck Sharp &Dohme Latvija » Skanstes 13, second floor, LV- 1013, Riga Latvia	Singulair mini 4 mg granulas	4 mg	Granules	Oral	

Member State	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Latvia	SIA « Merck Sharp &Dohme Latvija » Skanstes 13, second floor, LV- 1013, Riga Latvia	Singulair 4mg košļājamās tabletes	4 mg	Chewable tablets	Oral use	4 mg
Lithuania	"Merck Sharp & Dohme", UAB, Kestucio str. 59/27 LT-08124 Vilnius Lithuania	SINGULAIR MINI	4 mg	Granules	Oral	
Lithuania	"Merck Sharp & Dohme", UAB, Kestucio str. 59/27 LT-08124 Vilnius Lithuania	SINGULAIR	4 mg	Chewable tablets	Oral use	4 mg
Luxembourg	Merck Sherp & Dohme Chaussée de Waterloo 1135 B-1180 Brussels Belgium	SINGULAIR MINI	4 mg	Granules	Oral	
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B- 1180 Brussels Belgium	SINGULAIR	4 mg	Chewable tablets	Oral use	4 mg
Malta	Merck Sharp & Dohme Hertfordshire Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	Singulair Paediatric 4mg Granules	4mg	Granules	Oral	
Malta	Merck Sharp & Dohme Hertfordshire Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	Singulair Paediatric 4mg	4mg	Chewable Tablets	Oral use	4 mg

Member State	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
The Netherlands	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem, The Netherlands	Singulair Kleuter	4 mg	Chewable tablets	Oral use	4 mg
Norway	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Granules	Oral	
Norway	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Chewable tablets	Oral use	4 mg
Poland	MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warszawa Poland	SINGULAIR 4	4 mg	Chewable tablets	Oral use	4 mg
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	Singulair Infantil 4 mg Granulado	4 mg	Granules	Oral	
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	Singulair Infantil	4 mg	Chewable tablets	Oral use	4 mg

Member State	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Romania	MERCK SHARP & DOHME ROMANIA S.R.L. Bucharest Business Park Şos. Bucureşti-Ploieşti, nr. 1A, Corp clădire C1, Etaj 3, Sector 1, Bucureşti Romania	SINGULAIR, granule, 4 mg/plic	4 mg	Granules	Oral	
Romania	MERCK SHARP & DOHME ROMANIA S.R.L. Bucharest Business Park Şos. Bucureşti-Ploieşti, nr.1A, Corp clădire C1, Etaj 3, Sector 1, Bucureşti Romania	SINGULAIR 4 mg, comprimate masticabile	4 mg	Chewable tablets	Oral use	4 mg
Slovenia	Merck Sharp & Dohme, Smartinska 140, SI-1000 Ljubljana Slovenia	Singulair 4 mg zrnca	4 mg	Granules	Oral	
Slovenia	Merck Sharp & Dohme, Smartinska 140, SI-1000 Ljubljana Slovenia	Singulair 4 mg zvecljive tablete	4 mg	Chewable tablets	Oral use	4 mg
Slovak Republic	Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem P.O. Box 581, 2003 PC Haarlem The Netherlands	SINGULAIR 4 mg	4 mg	Chewable tablets	Oral use	4 mg

Member State	Marketing Authorisation Holder	(Invented) name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Spain	Merck Sharp and Dohme de España, SA Josefa Valcarcel, 38 28027 – Madrid Spain	Singulair 4 mg granulado	4 mg	Granules	Oral	
Spain	Merck Sharp and Dohme de España, SA Josefa Valcarcel, 38 28027- Madrid Spain	Singulair 4 mg comprimidos masticables	4 mg	Chewable tablets	Oral use	4 mg
Sweden	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Granules	Oral	
Sweden	Merck Sharp & Dohme B.V., Postbox 581, Waarderweg 39, NL-2031 BN, Haarlem The Netherlands	Singulair	4 mg	Chewable tablets	Oral use	4 mg
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, the United Kingdom	Singulair Paediatric 4mg Granules	4mg	Granules	Oral use	
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, the United Kingdom	Singulair Paediatric 4mg Chewable Tablets	4mg	Chewable Tablets	Oral use	4 mg

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SINGULAIR AND ASSOCIATED NAMES (SEE ANNEX I)

The present referral procedure sought harmonisation of the product information for Singulair 4 mg chewable tablets and 4 mg oral granules with the indications already approved for children 2-5 years old and 6 months to 2 years old in Mutual Recognition Procedures, with Finland acting as the reference member state. Simultaneously, the MAH updated module 3 was updated to CTD format in this referral procedure.

The active substance in Singulair products is montelukast sodium. It is a leukotriene-1 receptor antagonist. Montelukast sodium has been used for the add-on treatment (concomitantly with inhaled steroids) and to prevent exercise-induced bronchoconstriction.

Formulations for paediatric use, 4 mg chewable tablets and 4 mg oral granules, have been available since 2000 and 2002, respectively. Since 2002, the MRP indications also include the monotherapy of 4 mg paediatric formulations in the treatment of mild asthma in exceptional cases, i.e. when inhaled corticosteroids cannot be used.

Singulair 4 mg chewable tablets is available in all current EU member states (and in IS and NO) except in FR since the approval given in Mutual Recognition Procedure in 2000. Singulair 4 mg oral granules was approved by 16 member states (not by AT, BE, CZ, DK, FR, HU, NL, PL, SK) in MRP in 2002. Also IS and NO have granted marketing authorisation to this formulation.

Quality
The MAH provided harmonised modules 3 in CTD format for Singulair 4 mg granules and 4 mg chewable tablets. Moreover the MAH submitted a proposal for harmonised chemical-pharmaceutical sections of the SPC and PL.

SPC Harmonisation
The MAH selected the sections which presented major divergences and were the scope of the harmonisation through the referral procedure. All other sections of the SPCs will be harmonised as approved in the Mutual Recognition Procedure.

The following sections of the SPCs were presented for harmonisation: 4.1 Therapeutic Indications, 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special Warnings and Precautions for Use, 4.8 Undesirable effects, and 6.5 Shelf life.

The SPCs proposed by the MAH were those approved through the MRP in the "old" member states and in CY and IS. The indications given in these SPCs are the most restrictive among the approved indications in EU member states, and are approved in the most number of countries.

Furthermore, the latest variation procedure was finalised on 10th September 2007, and the SPCs that were then approved are in line with the proposals of the MAH in this referral.

Clinical Efficacy: Add-on use

Singulair is indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma, in patients aged 6 months to 5 years.

The Applicant/MAH provided supportive documentation for this indication of 4mg OG in children aged 6 month to 2 years based on pharmacokinetic data PN 136/138, supportive safety data PN 176, and the extrapolation of efficacy to this age group from the efficacy demonstrated in older children (2-5 years old, 6-14 years old) according to ICH E11 guideline. Further efficacy reports of two clinical

studies (P176 and P072-02; double-blind, randomized, placebo-controlled, parallel group) were presented for both 4mg OG and CT formulations. Montelukast showed improvement in the variables of asthma as compared to placebo. The effect of montelukast on asthma was modest, but consistent across the spectrum of variables, and in line with results obtained from studies on adults and older children.

The Applicant/MAH also made reference to an original application concerning the 10 mg film-coated tablet and 5 mg CT, which presents the results of two placebo-controlled clinical studies in more than 1600 adult patients with mild-to-moderate asthma. Montelukast (10 mg once daily at bedtime) was shown to improve respiratory functions, reduce asthma symptoms and beta-agonist use, and to improve quality of life as compared to placebo. In three active-controlled studies, in nearly 1000 adult patients with mild-to-moderate asthma, the effect of montelukast (10 mg once daily) was shown to be better than that obtained with placebo, but less than that obtained with inhaled beclometasone dipropionate (400 µg/day).

The Applicant/MAH also made reference to an original application concerning 5 mg CT, which presented the results of a study in 336 paediatric patients (age 6 to 14 years). Montelukast (5 mg once daily) was shown to exert an anti-asthmatic effect that was larger than the effect obtained with placebo. However, there were no data of studies comparing montelukast with active treatments in paediatric patients.

Given that the efficacy data from children aged 6 months to 2 years of age is not considered very robust, the CHMP requested, that the Applicant/MAH should give a more detailed instruction in Section 4.2 as to how the treatment effect should be monitored and evaluated. The following revision to Section 4.2 of Singulair 4 mg OG SPC was finally accepted:

Efficacy data from clinical trials in paediatric patients 6 months to 2 years of age with persistent asthma are limited. Patients should be evaluated after 2 to 4 weeks for response to montelukast. Treatment should be discontinued if lack of response is observed.

Subsequently, Section 4.4 of Singulair 4mg OG SPC was revised to include the following wording:

The diagnosis of persistent asthma in very young children (6 months – 2 years) should be established by a paediatrician or pulmonologist.

After careful deliberations, the CHMP considered that the clinical data to support the add-on therapy in very young children are sufficient for approval, taking into account that this formulation was approved for use in children aged 6 months to 2 years in approximately 52 countries, including 17 of 27 European Union (EU) Member States (first approval in 2002) plus Iceland and Norway. In a trend voting after the Applicant/MAH's Oral Explanation, the majority of the CHMP (26+2 positive, 3 negative votes) was in favour of accepting the indication as proposed by the Applicant/MAH, including the treatment of very young patients (6 months to 2 year old) when diagnosis of persistent asthma has been established.

Therefore, the CHMP agreed with the following proposed indication for 4mg chewable tablets:

"SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma".

The CHMP agreed with the following proposed indication for 4mg oral granules:

"SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 6 months to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma".

Clinical Efficacy: Monotherapy of asthma

Singulair may also be an alternative treatment option to low-dose inhaled corticosteroids for patients (4 mg OG, CT: 2 to 5 year old) with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.

Two long term studies to support the monotherapy indication were presented. Both were of double-blind, randomised, parallel-group type. Study P910 (treatment duration 52 weeks) was carried out in 6 to 14-year old paediatric patients, study P907 in patients 2 to 6 years old. The results of P910 suggest that with montelukast, as good benefit-risk ratio can be achieved in the treatment of paediatric mild, persistent asthma as with inhaled fluticasone. The treatment effect by montelukast is smaller than that achieved with fluticasone, but the difference is small enough to be clinically not significant, and it can be compensated with better treatment compliance due to oral, once daily administration of montelukast as opposed to twice-daily inhalation of fluticasone. Lack of effect on growth rate is also a benefit of montelukast. Results of P907 showed efficacy over placebo.

Given the lack of efficacy data for this indication in patients younger than 2 years, the CHMP consulted with the Paediatric Committee regarding the extrapolation of data from studies conducted in older paediatric patients to assess the safety/efficacy of montelukast in very young paediatric patients. The PDCO, basing its decision on the GINA paediatric handbook 2006 and expert intervention, concluded that, due to a shortage of clinical data in patients aged 6 months – 2 years with asthma, pharmacokinetic data from patients aged 2-5 years diagnosed with asthma cannot be extrapolated to younger patients aged 6 months- 2 years presenting with the same symptoms. The wheezing observed in the younger age group could be attributed to a number of diagnoses (viral infection, RSV bronchiolitis, or early symptoms of classic asthma). Therefore, the PDCO expressed the need to conduct studies to precisely define the patient population that should receive montelukast sodium for the treatment of mild persistent asthma.

However, the Applicant/MAH only seeks to maintain the indication for montelukast as monotherapy in mild to moderate persistent asthma in children aged 2 years to 5 years. Therefore, the CHMP agreed with the following proposed indication for 4mg chewable tablets and 4mg oral granules:

"Singulair may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids"

Clinical Efficacy: Exercise-induced asthma

Singulair is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

In double-blind, randomised studies it was also shown that the anti-asthmatic effect of montelukast can be shown against exercise-induced asthma in adults. The effect was seen over 12 weeks of therapy. There were no gender or race-related differences in the effect. In a small study on 27 paediatric patients it was also shown that montelukast seems to protect paediatric patients against exercise-induced broncho-constriction. This indication with regard to younger paediatric patients is largely based on these data, taking into account the pharmacokinetics of montelukast (rapid absorption) and data in adults showing the rapid onset of effect.

Given that activity limitation due to asthma is difficult to assess in very young children (aged < 2 years), the Applicant/MAH revised the indication to state that it refers only to children 2 years of age or older. Therefore the final revised indication for 4mg CT and 4mg OG is as follows:

"Singulair is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction".

Additionally, the CHMP requested, that the Applicant/MAH should give a more detailed instruction in Section 4.2 as to how the treatment effect should be monitored and evaluated. The following wording was therefore accepted for Section 4.2, 4 mg CT and 4 mg OG:

SINGULAIR as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction.
In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered."

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling, package leaflet and Module 3.

- the Summaries of Products Characteristic, labelling, package leaflet and Module 3 proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

- the CHMP concluded that the Marketing Authorisation could be harmonised for Singulair 4mg Granules (previously known as Oral Granules) for patients aged 6 months to 5 years on the following indications:

- SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 6 months to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma.

- SINGULAIR may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.2).

- SINGULAIR is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

- the CHMP concluded that the Marketing Authorisation could be harmonised for Singulair 4mg Chewable Tablets for patients aged 2 to 5 years on the following indications:

- SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma.

- SINGULAIR may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of

serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.2).

- SINGULAIR is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

the CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Singulair and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SINGULAIR 4 mg granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet of granules contains montelukast sodium, which is equivalent to 4 mg montelukast.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules.

White granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 6 months to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma.

SINGULAIR may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.2).

SINGULAIR is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

This medicinal product is to be given to a child under adult supervision. The dosage for paediatric patients 6 months to 5 years of age is one sachet of 4 mg granules daily to be taken in the evening. No dosage adjustment within this age group is necessary. Efficacy data from clinical trials in paediatric patients 6 months to 2 years of age with persistent asthma are limited. Patients should be evaluated after 2 to 4 weeks for response to montelukast treatment. Treatment should be discontinued if a lack of response is observed. The SINGULAIR 4 mg granules formulation is not recommended below 6 months of age.

Administration of SINGULAIR granules:
SINGULAIR granules can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft food (e.g., applesauce, ice cream, carrots and rice). The sachet should not be opened until ready to use. After opening the sachet, the full dose of SINGULAIR granules must be administered immediately (within 15 minutes). If mixed with food, SINGULAIR granules must not be stored for future use. SINGULAIR granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. SINGULAIR granules can be administered without regard to the timing of food ingestion.

General recommendations. The therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day. Patients should be advised to continue taking SINGULAIR even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

SINGULAIR as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma:
Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children 2 to 5 years old with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less that once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

SINGULAIR as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction.
In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.

Therapy with SINGULAIR in relation to other treatments for asthma.
When treatment with SINGULAIR is used as add-on therapy to inhaled corticosteroids, SINGULAIR should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

10 mg film-coated tablets are available for adults 15 years of age and older.
5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.
4 mg chewable tablets are available as an alternative formulation for paediatric patients 2 to 5 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The diagnosis of persistent asthma in very young children (6 months – 2 years) should be established by a paediatrician or pulmonologist.

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

4.5 Interactions with other medicinal products and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

4.6 Pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between SINGULAIR and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

SINGULAIR may be used during pregnancy only if it is considered to be clearly essential.

Use during lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known if montelukast is excreted in human milk.

SINGULAIR may be used in breast-feeding mothers only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:
- 10 mg film-coated tablets in approximately 4000 adult patients 15 years of age and older
- 5 mg chewable tablets in approximately 1750 paediatric patients 6 to 14 years of age
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age, and
- 4 mg granules in 175 paediatric patients 6 months to 2 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	**Adult Patients 15 years and older (two 12-week studies; n=795)**	**Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)**	**Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)**	**Paediatric Patients 6 months up to 2 years old (one 6-week study; n=175)**
Nervous system disorders	headache	headache		hyperkinesia
Respiratory, thoracic, and mediastinal disorders				asthma
Gastrointestinal disorders	abdominal pain		abdominal pain	diarrhoea
Skin and subcutaneous tissue disorders				eczematous dermatitis, rash
General disorders and administration site conditions			thirst	

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.
Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.
The safety profile in paediatric patients 6 months to 2 years of age did not change with treatment up to 3 months.

The following adverse reactions have been reported in post-marketing use:
Blood and lymphatic system disorders: increased bleeding tendency.

Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.
Psychiatric disorders: dream abnormalities including nightmares, hallucinations, insomnia, psychomotor hyperactivity (including irritability, restlessness, agitation including aggressive behaviour, and tremor), depression, suicidal thinking and behaviour (suicidality) in very rare cases.
Nervous system disorders: dizziness drowsiness, paraesthesia/hypoesthesia, seizure.
Cardiac disorders: palpitations.
Gastrointestinal disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.
Hepatobiliary disorders: elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis.
Skin and subcutaneous tissue disorders: angiooedema, bruising, urticaria, pruritus, rash, erythema nodosum.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.
General disorders and administration site conditions: asthenia/fatigue, malaise, oedema.
Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients (see section 4.4).

4.9 Overdose

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialyzable by peritoneal- or hemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist
ATC-code: R03D C03

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV_1: 7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclomethasone achieved an improvement in FEV_1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" β-agonist use (-11.7% vs +8.2% change from baseline).

In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior.
Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:
FEV_1 increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV_1 was significant: -2.2% with a 95% CI of -3.6, -0.7.
The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β-agonist use was significant: 2.7 with a 95% CI of 0.9, 4.5.
The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3% with a 95%CI of 2.9; 11.7.

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. Montelukast also decreased "as-needed" β-agonist use and

corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥3 consecutive days with daytime symptoms requiring β-agonist use, or corticosteroids (oral or inhaled), or hospitalization for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

Efficacy of montelukast is supported in paediatric patients 6 months to 2 years of age by extrapolation from the demonstrated efficacy in patients 2 years of age and older with asthma, and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the medicinal products's effect are substantially similar among these populations.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients 6 to 14 years of age (maximal fall in FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption. Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the C_{max} is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

The 4 mg granule formulation is bioequivalent to the 4 mg chewable tablet when administered to adults in the fasted state. In paediatric patients 6 months to 2 years of age, C_{max} is achieved 2 hours after administration of the 4 mg granules formulation. C_{max} is nearly 2-fold greater than in adults receiving a 10 mg tablet. The co-administration of applesauce or a high-fat standard meal with the granule formulation did not have a clinically meaningful effect on the pharmacokinetics of montelukast as determined by AUC (1225.7 vs 1223.1 ng•hr/mL with and without applesauce, respectively, and 1191.8 vs 1148.5 ng•hr/mL with and without a high-fat standard meal, respectively).

Distribution. Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation. Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination. The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

Characteristics in Patients. No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold based on systemic exposure).

Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Hyprolose (E 463)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Packaged in polyethylene/aluminum/polyester sachet in:
Cartons of 7, 20, 28 and 30 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

[To be completed nationally.]

8. MARKETING AUTHORIZATION NUMBER

[TO BE COMPLETED NATIONALLY.]

9. DATE OF first AUTHORIZATION/RENEWAL OF the AUTHORIZATION

[To be completed nationally.]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

SINGULAIR 4 MG CHEWABLE TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONE CHEWABLE TABLET CONTAINS MONTELUKAST SODIUM, WHICH IS EQUIVALENT TO 4 MG MONTELUKAST.

EXCIPIENT: ASPARTAME (E 951) 1.2 MG PER TABLET.

FOR A FULL LIST OF EXCIPIENTS, SEE SECTION 6.1.

3. PHARMACEUTICAL FORM

CHEWABLE TABLET.

Pink, oval, bi-convex-shaped, SINGULAIR engraved on one side and MSD 711 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SINGULAIR is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma.

SINGULAIR may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.2).

SINGULAIR is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

This medicinal product is to be given to a child under adult supervision. For children who have problems consuming a chewable tablet, a granule formulation is available (see SINGULAIR 4 mg granule SPC). The dosage for paediatric patients 2-5 years of age is one 4 mg chewable tablet daily to be taken in the evening. If taken in connection with food, SINGULAIR should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary. The SINGULAIR 4 mg chewable tablet formulation is not recommended below 2 years of age.

General recommendations. The therapeutic effect of SINGULAIR on parameters of asthma control occurs within one day. Patients should be advised to continue taking SINGULAIR even if their asthma is under control, as well as during periods of worsening asthma.

No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.

SINGULAIR as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma:
Montelukast is not recommended as monotherapy in patients with moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids (see section 4.1). Mild persistent asthma is defined as asthma symptoms more than once a week but less that once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.

SINGULAIR as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction.
In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.

Therapy with SINGULAIR in relation to other treatments for asthma.
When treatment with SINGULAIR is used as add-on therapy to inhaled corticosteroids, SINGULAIR should not be abruptly substituted for inhaled corticosteroids (see section 4.4).

10 mg film-coated tablets are available for adults 15 years of age and older.
5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.
4 mg granules are available for paediatric patients 6 months to 5 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Patients should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.

Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.

There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.

In rare cases, patients on therapy with anti-asthma agents including montelukast may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases usually, but not always, have been associated with the reduction or withdrawal of oral corticosteroid therapy. The possibility that leukotriene receptor antagonists may be associated with emergence of Churg-Strauss syndrome can neither be excluded nor established. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.

SINGULAIR contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 4 mg chewable tablet contains phenylalanine in an amount equivalent to 0.674 mg phenylalanine per dose.

4.5 Interactions with other medicinal products and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products:theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, such as phenytoin, phenobarbital and rifampicin.

In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 *in vivo.* Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)

4.6 Pregnancy and lactation

Use during pregnancy

Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development.

Limited data from available pregnancy databases do not suggest a causal relationship between SINGULAIR and malformations (i.e. limb defects) that have been rarely reported in worldwide post marketing experience.

SINGULAIR may be used during pregnancy only if it is considered to be clearly essential.

Use during lactation

Studies in rats have shown that montelukast is excreted in milk (see section 5.3). It is not known if montelukast is excreted in human milk.

SINGULAIR may be used in breast-feeding mothers only if it is considered to be clearly essential.

4.7 Effects on ability to drive and use machines

Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies as follows:

- 10 mg film-coated tablets in approximately 4000 adult patients 15 years of age and older
- 5 mg chewable tablets in approximately 1750 paediatric patients 6 to 14 years of age, and
- 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.

The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56 week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	headache	headache	
Gastrointestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.
Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.

The following adverse reactions have been reported in post-marketing use:
Blood and lymphatic system disorders: increased bleeding tendency.
Immune system disorders: hypersensitivity reactions including anaphylaxis, hepatic eosinophilic infiltration.
Psychiatric disorders: dream abnormalities including nightmares, hallucinations, insomnia, psychomotor hyperactivity (including irritability, restlessness, agitation including aggressive behaviour, and tremor), depression, suicidal thinking and behaviour (suicidality) in very rare cases.
Nervous system disorders: dizziness drowsiness, paraesthesia/hypoesthesia, seizure.
Cardiac disorders: palpitations.
Gastrointestinal disorders: diarrhoea, dry mouth, dyspepsia, nausea, vomiting.
Hepatobiliary disorders: elevated levels of serum transaminases (ALT, AST), cholestatic hepatitis.
Skin and subcutaneous tissue disorders: angiooedema, bruising, urticaria, pruritus, rash, erythema nodosum.
Musculoskeletal and connective tissue disorders: arthralgia, myalgia including muscle cramps.
General disorders and administration site conditions: asthenia/fatigue, malaise, oedema.
Very rare cases of Churg-Strauss Syndrome (CSS) have been reported during montelukast treatment in asthmatic patients (see section 4.4).

4.9 Overdose

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg

(approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialyzable by peritoneal- or hemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Leukotriene receptor antagonist
ATC-code: R03D C03

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.

In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.

Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV_1: 7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated with beclomethasone achieved an improvement in FEV_1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).

In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. Montelukast also decreased "as-needed" β-agonist use and

corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.

In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥3 consecutive days with daytime symptoms requiring β-agonist use, or corticosteroids (oral or inhaled), or hospitalization for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.

In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" β-agonist use (-11.7% vs +8.2% change from baseline).

In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior.
Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:
FEV_1 increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV_1 was significant: -2.2% with a 95% CI of -3.6, -0.7.
The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β-agonist use was significant: 2.7 with a 95% CI of 0.9, 4.5.
The percentage of patients with an asthma attack (an asthma attack being defined as a period of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3% with a 95%CI of 2.9; 11.7.

Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients 6 to 14 years of age (maximal fall in FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.

In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption. Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal. Safety and efficacy were demonstrated in clinical trials where the 10 mg film-coated tablet was administered without regard to the timing of food ingestion.

For the 5 mg chewable tablet, the C_{max} is achieved in 2 hours after administration in adults in the fasted state. The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.

Distribution. Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours post-dose were minimal in all other tissues.

Biotransformation. Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.

Elimination. The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

Characteristics in Patients. No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score >9).

With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete

ossification, compared with concurrent control animals, was seen at systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold based on systemic exposure).

Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Hyprolose (E 463)
Red ferric oxide (E 172)
Croscarmellose sodium
Cherry flavour
Aspartame (E 951)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Packaged in polyamide/PVC/aluminum blister package in:
.
Blisters in packages of: 7, 10, 14, 20, 28, 30, 50, 56, 98, 100, 140 and 200 tablets.
Blisters (unit doses), in packages of: 49, 50 and 56 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

[TO BE COMPLETED NATIONALLY]

8. MARKETING AUTHORIZATION NUMBER

[TO BE COMPLETED NATIONALLY]

9. DATE OF first AUTHORIZATION/RENEWAL OF the AUTHORIZATION

[TO BE COMPLETED NATIONALLY]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SINGULAIR 4 mg Granules– Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

SINGULAIR 4 mg granules
montelukast
For children 6 months to 5 years of age

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One sachet of granules contains montelukast sodium, which is equivalent to 4 mg montelukast.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Granules
7 x 1 sachet
20 x 1 sachet
28 x 1 sachet
30 x 1 sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

SINGULAIR 4 mg granules

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGULAIR 4 mg Granules - Sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SINGULAIR 4 mg granules
montelukast

2. METHOD OF ADMINISTRATION

Oral use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sachet

6. OTHER

{Name of the Marketing Authorisation Holder}
[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SINGULAIR 4 mg Tablets – Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

SINGULAIR 4 mg chewable tablets
montelukast
For children 2 to 5 years of age

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One chewable tablet contains montelukast sodium, which is equivalent to 4 mg montelukast.

3. LIST OF EXCIPIENTS

Contains aspartame (E 951). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7, 10, 14, 20, 28, 30, 49, 50, 56, 98, 100, 140, 200 chewable tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

SINGULAIR 4 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

SINGULAIR 4 mg tablets - Blister

1. NAME OF THE MEDICINAL PRODUCT

SINGULAIR 4 mg chewable tablet

montelukast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

SINGULAIR 4 mg Granules
montelukast

Read all of this leaflet carefully before your child starts taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- 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:

1. What SINGULAIR is and what it is used for
2. Before SINGULAIR is taken
3. How to take SINGULAIR
4. Possible side effects
5. How to store SINGULAIR
6. Further information

1. WHAT SINGULAIR IS AND WHAT IT IS USED FOR

SINGULAIR is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in the lungs. By blocking leukotrienes, SINGULAIR improves asthma symptoms and helps control asthma.

Your doctor has prescribed SINGULAIR to treat your child's asthma, preventing asthma symptoms during the day and night.

- SINGULAIR is used for the treatment of 6 months to 5 year old patients who are not adequately controlled on their medication and need additional therapy.
- SINGULAIR may also be used as an alternative treatment to inhaled corticosteroids for 2 to 5 year old patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.
- SINGULAIR also helps prevent the narrowing of airways triggered by exercise for patients 2 years of age and older.

Your doctor will determine how SINGULAIR should be used depending on the symptoms and severity of your child's asthma.

What is asthma?

Asthma is a long-term disease.

Asthma includes:
- difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.
- sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
- swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: Coughing, wheezing, and chest tightness.

2. BEFORE SINGULAIR IS TAKEN

Tell your doctor about any medical problems or allergies your child has now or has had.

Do not give SINGULAIR to your child if he/she

- is allergic (hypersensitive) to montelukast or any of the other ingredients of SINGULAIR (see 6. FURTHER INFORMATION).

Take special care with SINGULAIR

- If your child's asthma or breathing gets worse, tell your doctor immediately.
- Oral SINGULAIR is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you for your child. Always have your child's inhaled rescue medicine for asthma attacks with you.
- It is important that your child take all asthma medications prescribed by your doctor. SINGULAIR should not be used instead of other asthma medications your doctor has prescribed for your child.
- If your child is on anti-asthma medicines, be aware that if the he/she develops a combination of symptoms such as flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash, you should consult your doctor.
- Your child should not take acetyl-salicylic acid (aspirin) or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make his/her asthma worse.

Taking other medicines

Some medicines may affect how SINGULAIR works, or SINGULAIR may affect how your child's other medicines work.

Please tell your doctor or pharmacist if your child is taking or has recently taken other medicines, including those obtained without a prescription.

Tell your doctor if your child is taking the following medicines before starting SINGULAIR:
- phenobarbital (used for treatment of epilepsy)
- phenytoin (used for treatment of epilepsy)
- rifampicin (used to treat tuberculosis and some other infections)

Taking SINGULAIR with food and drink

SINGULAIR granules can be taken without regard to the timing of food intake.

Pregnancy and breast-feeding

This subsection is not applicable for the SINGULAIR 4 mg granules since they are intended for use in children 6 months to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

Use in pregnancy

Women who are pregnant or intend to become pregnant should consult their doctor before taking SINGULAIR. Your doctor will assess whether you can take SINGULAIR during this time.

Use in breast-feeding

It is not known if SINGULAIR appears in breast milk. You should consult your doctor before taking SINGULAIR if you are breast-feeding or intend to breast-feed.

Driving and using machines

This subsection is not applicable for the SINGULAIR 4 mg granules since they are intended for use in children 6 months to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

SINGULAIR is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with SINGULAIR may affect some patients' ability to drive or operate machinery.

3. HOW TO TAKE SINGULAIR

- This medicine is to be given to a child under adult supervision. Your child should take SINGULAIR every evening.
- It should be taken even when your child has no symptoms or if he/she has an acute asthma attack.
- Always have your child take SINGULAIR as your doctor has told you. You should check with your child's doctor or pharmacist if you are not sure.
- To be taken by mouth

For children 6 months to 5 years of age:
One sachet of SINGULAIR 4 mg granules to be taken by mouth each evening.

If your child is taking SINGULAIR, be sure that your child does not take any other products that contain the same active ingredient, montelukast.

For children 6 months to 2 years old, SINGULAIR 4 mg granules are available.
For children 2 to 5 years old, SINGULAIR 4 mg chewable tablets and SINGULAIR 4 mg granules are available. The SINGULAIR 4 mg granules formulation is not recommended below 6 months of age.

How should I give SINGULAIR granules to my child?

- Do not open the sachet until ready to use.

- SINGULAIR granules can be given either:
  - directly in the mouth;
  - OR mixed with a spoonful of cold or room temperature soft food (for example, applesauce, ice cream, carrots and rice).

- Mix all of the contents of the SINGULAIR granules into a spoonful of cold or room temperature soft food, taking care to see that the entire dose is mixed with the food.

- Be sure the child is given the entire spoonful of the granule/food mixture immediately (within 15 minutes). IMPORTANT: Never store any granule/food mixture for use at a later time.

- SINGULAIR granules are not intended to be dissolved in liquid. However, your child may take liquids after swallowing the SINGULAIR granules.

- SINGULAIR granules can be taken without regard to the timing of food intake.

If your child takes more SINGULAIR than he/she should

Contact your child's doctor immediately for advice.

There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity.

If you forget to give SINGULAIR to your child

Try to give SINGULAIR as prescribed. However, if your child misses a dose, just resume the usual schedule of one sachet once daily.

Do not give a double dose to make up for a forgotten dose.

If your child stops taking SINGULAIR

SINGULAIR can treat your child's asthma only if he/she continues taking it.
It is important for your child to continue taking SINGULAIR for as long as your doctor prescribes. It will help control your child's asthma.

If you have any further questions on the use of this product, ask your child's doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

In clinical studies with SINGULAIR 4 mg granules, the most commonly reported side effects (occurring in at least 1 of 100 patients and less than 1 of 10 paediatric patients treated) thought to be related to SINGULAIR were:
- diarrhoea
- hyperactivity
- asthma
- scaly and itchy skin
- rash

Additionally, the following side effects were reported in clinical studies with either SINGULAIR 10 mg film-coated tablets, 5 mg or 4 mg chewable tablets:
- abdominal pain
- headache
- thirst

These were usually mild and occurred at a greater frequency in patients treated with SINGULAIR than placebo (a pill containing no medication).

Additionally, while the medicine has been on the market, the following have been reported:

- allergic reactions including rash, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, itching, and hives;
- tiredness, restlessness, agitation including aggressive behaviour, irritability, tremor, depression, suicidal thoughts and actions (in very rare cases), dizziness, drowsiness, hallucinations, dream abnormalities, including nightmares and trouble sleeping, pins and needles/numbness, seizure;
- feeling unwell, joint or muscle pain, muscle cramps, dry mouth, nausea, vomiting, indigestion, diarrhoea, hepatitis;
- increased bleeding tendency, bruising, tender red lumps under the skin most commonly on your shins (erythema nodosum), palpitations;
- swelling.

In asthmatic patients treated with montelukast, very rare cases of a combination of symptoms such as flu-like illness, pins and needles or numbness of arms and legs, worsening of pulmonary symptoms and/or rash (Churg-Strauss syndrome) have been reported. You must tell your doctor right away if your child gets one or more of these symptoms.

Ask your doctor or pharmacist for more information about 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 child's doctor or pharmacist.

5. HOW TO STORE SINGULAIR

- Keep out of the reach and sight of children.

- Do not use this medicine after the date shown by the six numbers following EXP on the sachet. The first two numbers indicate the month; the last four numbers indicate the year. This medicine expires at the end of the month shown.

- Store in the original package in order to protect from light and moisture.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What SINGULAIR contains

- The active substance is montelukast. Each sachet of granules contains montelukast sodium which corresponds to 4 mg of montelukast.
- The other ingredients are: Mannitol, hyprolose (E 463), and magnesium stearate.

What SINGULAIR looks like and contents of the pack

4 mg SINGULAIR granules are white granules.
Cartons of 7, 20, 28 and 30 sachets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder and Manufacturer	*Information is given by*
{To be completed nationally}	{To be completed nationally}

This medicinal product is authorized in the Member States of the EEA under the following names:

Bulgaria, Cyprus, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom:

SINGULAIR

Italy: MONTEGEN

This leaflet was last approved in {DD.MM.YYYY.}

PACKAGE LEAFLET: INFORMATION FOR THE USER

SINGULAIR 4 mg chewable tablets
montelukast

Read all of this leaflet carefully before your child starts taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- 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.

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- SINGULAIR is used for the treatment of 2 to 5 year old patients who are not adequately controlled on their medication and need additional therapy.
- SINGULAIR may also be used as an alternative treatment to inhaled corticosteroids for 2 to 5 year old patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.
- SINGULAIR also helps prevent the narrowing of airways triggered by exercise for patients 2 years of age and older.

Your doctor will determine how SINGULAIR should be used depending on the symptoms and severity of your child's asthma.

What is asthma?

Asthma is a long-term disease.

Asthma includes:
- difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.
- sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
- swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: Coughing, wheezing, and chest tightness.

2. BEFORE SINGULAIR IS TAKEN

Tell your doctor about any medical problems or allergies your child has now or has had.

Do not give SINGULAIR to your child if he/she

- is allergic (hypersensitive) to montelukast or any of the other ingredients of SINGULAIR (see 6. FURTHER INFORMATION).

Take special care with SINGULAIR

- If your child's asthma or breathing gets worse, tell your doctor immediately.
- Oral SINGULAIR is not meant to treat acute asthma attacks. If an attack occurs, follow the instructions your doctor has given you for your child. Always have your child's inhaled rescue medicine for asthma attacks with you.
- It is important that your child take all asthma medications prescribed by your doctor. SINGULAIR should not be used instead of other asthma medications your doctor has prescribed for your child.
- If your child is on anti-asthma medicines, be aware that if he/she develops a combination of symptoms such as flu-like illness, pins and needles or numbness of arms or legs, worsening of pulmonary symptoms, and/or rash, you should consult your doctor.
- Your child should not take acetyl-salicylic acid (aspirin) or anti-inflammatory medicines (also known as non-steroidal anti-inflammatory drugs or NSAIDs) if they make his/her asthma worse.

Taking other medicines

Some medicines may affect how SINGULAIR works, or SINGULAIR may affect how your child's other medicines work.

Please tell your doctor or pharmacist if your child is taking or has recently taken other medicines, including those obtained without a prescription.

Tell your doctor if your child is taking the following medicines before starting SINGULAIR:
- phenobarbital (used for treatment of epilepsy)
- phenytoin (used for treatment of epilepsy)
- rifampicin (used to treat tuberculosis and some other infections)

Taking SINGULAIR with food and drink

SINGULAIR 4 mg chewable tablets should not be taken immediately with food; they should be taken at least 1 hour before or 2 hours after food.

Pregnancy and breast-feeding
This subsection is not applicable for the SINGULAIR 4 mg chewable tablets since they are intended for use in children 2 to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

Use in pregnancy

Women who are pregnant or intend to become pregnant should consult their doctor before taking SINGULAIR. Your doctor will assess whether you can take SINGULAIR during this time.

Use in breast-feeding

It is not known if SINGULAIR appears in breast milk. You should consult your doctor before taking SINGULAIR if you are breast-feeding or intend to breast-feed.

Driving and using machines
This subsection is not applicable for the SINGULAIR 4 mg chewable tablets since they are intended for use in children 2 to 5 years of age, however the following information is relevant to the active ingredient, montelukast.

SINGULAIR is not expected to affect your ability to drive a car or operate machinery. However, individual responses to medication may vary. Certain side effects (such as dizziness and drowsiness) that have been reported very rarely with SINGULAIR may affect some patients' ability to drive or operate machinery.

Important information about some of the ingredients of SINGULAIR

SINGULAIR chewable tablets contain aspartame, a source of phenylalanine. If your child has phenylketonuria (a rare, hereditary disorder of the metabolism) you should take into account that each 4-mg chewable tablet contains phenylalanine (equivalent to 0.674 mg phenylalanine per 4 mg chewable tablet).

3. HOW TO TAKE SINGULAIR

- This medicine is to be given to a child under adult supervision. For children who have problems consuming a chewable tablet, an oral granule formulation is available.
- Your child should take only one tablet of SINGULAIR once a day as prescribed by your doctor.
- It should be taken even when your child has no symptoms or if he/she has an acute asthma attack.
- Always have your child take SINGULAIR as your doctor has told you. You should check with your child's doctor or pharmacist if you are not sure.
- To be taken by mouth

For children 2 to 5 years of age:
One 4 mg chewable tablet daily to be taken in the evening. SINGULAIR 4 mg chewable tablets should not be taken immediately with food; it should be taken at least 1 hour before or 2 hours after food.

If your child is taking SINGULAIR, be sure that he/she does not take any other medicines that contain the same active ingredient, montelukast.

For children 2 to 5 years old, SINGULAIR 4 mg chewable tablets and 4 mg granules are available. For children 6 to 14 years old, SINGULAIR 5 mg chewable tablets are available. The SINGULAIR 4 mg chewable tablet is not recommended below 2 years of age.

If your child takes more SINGULAIR than he/she should

Contact your child's doctor immediately for advice.

There were no side effects reported in the majority of overdose reports. The most frequently occurring symptoms reported with overdose in adults and children included abdominal pain, sleepiness, thirst, headache, vomiting, and hyperactivity.

If you forget to give SINGULAIR to your child

Try to give SINGULAIR as prescribed. However, if your child misses a dose, just resume the usual schedule of one tablet once daily.

Do not give a double dose to make up for a forgotten dose.

If your child stops taking SINGULAIR

SINGULAIR can treat your child's asthma only if he/she continues taking it.

It is important for your child to continue taking SINGULAIR for as long as your doctor prescribes. It will help control your child's asthma.

If you have any further questions on the use of this product, ask your child's doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

In clinical studies with SINGULAIR 4 mg chewable tablets, the most commonly reported side effects (occurring in at least 1 of 100 patients and less than 1 of 10 paediatric patients treated) thought to be related to SINGULAIR were:

- abdominal pain
- thirst

Additionally, the following side effect was reported in clinical studies with SINGULAIR 10 mg film-coated tablets and 5 mg chewable tablets:

- headache

These were usually mild and occurred at a greater frequency in patients treated with SINGULAIR than placebo (a pill containing no medication).

Additionally, while the medicine has been on the market, the following have been reported:

- allergic reactions including rash, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, itching, and hives;
- tiredness, restlessness, agitation including aggressive behaviour, irritability, tremor, depression, suicidal thoughts and actions (in very rare cases), dizziness, drowsiness, hallucinations, dream abnormalities, including nightmares and trouble sleeping, pins and needles/numbness, seizure;
- feeling unwell, joint or muscle pain, muscle cramps, dry mouth, nausea, vomiting, indigestion, diarrhoea, hepatitis;
- increased bleeding tendency, bruising, tender red lumps under the skin most commonly on your shins (erythema nodosum), palpitations;
- swelling.

In asthmatic patients treated with montelukast, very rare cases of a combination of symptoms such as flu-like illness, pins and needles or numbness of arms and legs, worsening of pulmonary symptoms

and/or rash (Churg-Strauss syndrome) have been reported. You must tell your doctor right away if your child gets one or more of these symptoms.

Ask your doctor or pharmacist for more information about 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 child's doctor or pharmacist.

5. HOW TO STORE SINGULAIR

- Keep out of the reach and sight of children.
- Do not use this medicine after the date shown by the six numbers following EXP on the blister. The first two numbers indicate the month; the last four numbers indicate the year. This medicine expires at the end of the month shown.
- Store in the original package in order to protect from light and moisture.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What SINGULAIR contains

- The active substance is montelukast. Each tablet contains montelukast sodium which corresponds to 4 mg of montelukast.
- The other ingredients are:

  Mannitol, microcrystalline cellulose, hyprolose (E 463), red ferric oxide (E 172), croscarmellose sodium, cherry flavour, aspartame (E951), and magnesium stearate.

What SINGULAIR looks like and contents of the pack

4 mg SINGULAIR chewable tablets are pink, oval, biconvex with SINGULAIR engraved on one side and MSD 711 on the other.
Blisters in packages of: 7, 10, 14, 20, 28, 30, 50, 56, 98, 100, 140 and 200 tablets.
Blisters (unit doses), in packages of: 49, 50 and 56 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder and Manufacturer	*Information is given by*
{To be completed nationally}	{To be completed nationally}

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain, Sweden, United Kingdom

SINGULAIR

This leaflet was last approved in {DD.MM.YYYY.}