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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Review under Article 5(3) of Regulation (EC) No 726/2004

Desloratadine-containing medicinal products

Procedure no: EMEA/H/A-5(3)/1431

Note:

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

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# 1. Information on the procedure

In the context of a national procedure for a medicinal product containing desloratadine, the prescription status of desloratadine-containing products authorised nationally in Germany had been challenged by a marketing authorisation holder. The German national competent authority (BfArM) had previously declined a switch of the prescription status of nationally-authorised desloratadine-containing products from 'medicinal products subject to prescription' (also known as POM – prescription-only medicines) to 'medicinal products not subject to prescription' (also known as OTC – over-the-counter). The rationale for the BfArM decision was that medicinal products containing the same strength, pharmaceutical form, indication and active substance but differing with regards to the prescription status cannot be accepted on the German market for safety reasons. In this respect, the existing centrally-authorised products set a precedent as they are classified as subject to medical prescription.

An administrative court ruling supported the BfArM position but referred to the possibility for BfArM to engage on a discussion for a potential switch of legal status to OTC for the desloratadine-containing products authorised in the centralised procedure.

On 16 December 2015, BfArM requested a scientific opinion by the CHMP under Art 5(3) of Regulation (EC) No 726/2004, on whether desloratadine-containing products should be switched to non-prescription status.

## 2. Scientific Discussion

### 2.1. Introduction

Desloratadine is a non-sedating long-acting histamine (H) antagonist with potent selective, peripheral H1-receptor antagonist activity. Desloratadine is the primary active metabolite of loratadine, which has been widely available in the majority of Member States as an OTC-medicinal product for a number of years.

Desloratadine is approved in different formulations to treat symptoms associated with allergic rhinitis and urticaria. The originator desloratadine product is available in the following formulations:

- 5 mg film-coated tablet and 5 mg orodispersible tablet (adults and adolescents aged 12 years and older);
- 2.5 mg orodispersible tablet (adults, adolescents aged 12 years and older and children aged 6 – 11 years old);
- 0.5 mg/ml oral solution (adults, adolescents and children over the age of 1 year).

While the centrally authorised originator product is subject to medical prescription, in a few Member States some of the nationally approved products containing desloratadine have been authorised under OTC status (BG, DK, EE, FI, HU, LT, LV, NO, PL and SE). The existing OTC products differ slightly between Member States with regards to therapeutic indication, age limits, restriction of duration of use (after which a physician should be consulted if symptoms do not improve or worsen), some other elements of the product information and pack size.

In order to address the question of whether desloratadine-containing products could be switched to non-prescription status, the CHMP consulted the marketing authorisation holder of the centrally

authorised originator product (Aerius) and considered data included in the marketing authorisation dossier for Aerius, as well as information from reports drafted by Member States when assessing either the switch of legal status from prescription to OTC or the granting of a marketing authorisation for desloratadine-containing products under OTC status.

Article 71 of Directive 2001/83/EC states the conditions for classifying a medicinal product as subject to medical prescription. Thus a medicinal product which meets these criteria would be subject to medical prescription and a medicinal product which does not meet these criteria would not be subject to medical prescription. These criteria are further clarified in the European Commission's Guideline on changing the classification for the supply of a medicinal product for human use (Rev. January 2006)<sup>1</sup>.

## **2.2. Non-clinical aspects**

Desloratadine is the main active metabolite of loratadine. It is a more potent H1 receptor antagonist than loratadine itself and in most preclinical studies the AUC was higher after desloratadine administration than after an equimolar dose of loratadine. The practical consequence is that desloratadine can be used at a 5 mg/day dose, compared to 10 mg/day for loratadine.

Non-clinical studies conducted with desloratadine and loratadine could not identify qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine at comparable levels of exposure.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. The lack of carcinogenic potential was demonstrated in studies conducted with desloratadine and loratadine.

## **2.3. Clinical aspects**

### **2.3.1. Pharmacokinetics**

The metabolism of loratadine goes through 2 pathways. In normal metabolizers, more than 90% of loratadine is converted to desloratadine through the first pathway. Through the second pathway, which is considered the minor one, loratadine is converted to 3-OH-desloratadine.

There are pharmacokinetic differences between loratadine and desloratadine.

#### **2.3.1.1. ADME**

Pharmacokinetic parameters are different between both molecules, which is to be expected as desloratadine is the descarboethoxy oxidized loratadine, leading to a less lipophilic compound in comparison with loratadine.

Loratadine achieves a T<sub>max</sub> between 1-1.5h after administration whereas the observed T<sub>max</sub> after administration of desloratadine is approximately 3h. After administration of 10 mg loratadine, peak plasma concentrations (C<sub>max</sub>) of 13 nM and 12 nM have been noted for loratadine and desloratadine, respectively. After administration of 5 mg desloratadine, a C<sub>max</sub> value of 7 nM has been observed.

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<sup>1</sup> Guideline on changing the classification for the supply of a medicinal product for human use (Rev. January 2006). European Commission, Brussels, 2006. Available from URL: [http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/switchguide\\_160106\\_en.pdf](http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/switchguide_160106_en.pdf)

Loratadine is characterised by an extremely variable disposition. In adult volunteers, the fraction of the dose eliminated unchanged ranges from less than 1% to greater than 60%, and up to nine-fold difference in total body clearance is reported.

The metabolic conversion of loratadine into desloratadine involves both CYP3A4 and CYP2D6, which is variably expressed in the population.

In a randomised multiple-dose study comparing the steady state pharmacokinetic profiles following oral administration of 5 mg (once daily) desloratadine with those obtained following multiple dose administration of 10 mg loratadine (once daily), plasma concentrations of desloratadine, 3-OH-desloratadine and 3-OH-desloratadine glucuronide were observed to be very similar<sup>2</sup>.

The mean ratio of AUCs of desloratadine to loratadine in human plasma ranged from 5.2±4.0 for a single dose of 30 mg loratadine to 7.2±9.6 after a single dose of 10 mg loratadine. In steady-state conditions, the ratio appeared to be 6.7.

It has been established that some individuals have an impaired ability to form the active metabolite of desloratadine. A genetic polymorphism in the metabolism of desloratadine was observed in 8.6% of the population evaluated in the clinical pharmacology studies. The frequency of slow metabolisers is estimated to be about 4-6%. In slow metabolisers, median AUC values were approximately 6-fold higher, with reported C<sub>max</sub> values 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. The major route of elimination by a slow metaboliser is via excretion of unchanged drug into urine and faeces. The amount of 3-OH-desloratadine and unchanged drug is less than 10% and over 42% respectively compared to 51% and 8.4% in normal metabolisers. Recent information<sup>3</sup> elucidated this mechanism: glucuronidation by UGT2B10 followed by CYP2C8 oxidation and a non-enzymatic deconjugation. It is important to note that both UGT2B10 and CYP2C8 are characterised by genetic polymorphisms, which are described to be highly population dependent. In addition, these polymorphisms could have clinical significant consequences. It is possible that these polymorphisms are at the base of the formerly observed polymorphism in the metabolism of desloratadine. As almost all loratadine is metabolised to desloratadine, it would be expected that slow metabolisers of desloratadine would also present with these significant higher exposures to desloratadine after the administration of loratadine, especially in view of the long experience with loratadine. However, further clinical studies with desloratadine showed that this phenotype was not associated with higher adverse event reporting, and therefore, the absence of any data reporting higher exposure to desloratadine after administration of loratadine in slow metabolisers of desloratadine, is probably devoid of any clinical relevance.

### **2.3.1.2. Interactions**

As mentioned above, the metabolism of loratadine to desloratadine involves both CYP3A4 and CYP2D6, two isoenzymes that are prone to drug-drug interactions.

Desloratadine is less lipophilic, and hence more soluble than loratadine, and this could be the reason why it has a lower affinity for the binding site of P-glycoprotein (P-gp). Indeed, the functional inhibition of P-gp by desloratadine is much lower than that of loratadine, as measured by both extent and affinity (4-fold). Desloratadine therefore is not a significant inhibitor of P-gp and should not cause clinical drug

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<sup>2</sup> Aeriis: EPAR - Scientific discussion. Available from URL: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Scientific\\_Discussion/human/000313/WC500022748.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000313/WC500022748.pdf)

<sup>3</sup> Kazmi F. et al. A Long-Standing Mystery Solved: The Formation of 3-Hydroxydesloratadine Is Catalyzed by CYP2C8 But Prior Glucuronidation of Desloratadine by UDP-Glucuronosyltransferase 2B10 Is an Obligatory Requirement. *Drug Metab Dispos* 2015

interactions with agents that are P-gp substrates. Although loratadine is not expected to exhibit significant interactions at clinically relevant doses, this could be different when higher doses are taken.

### **2.3.1.3. Special populations**

A dedicated Phase 1 study in 37 subjects (12 healthy subjects, 25 patients with chronic renal insufficiency) showed a 1.5-2.5 fold increase in AUC for desloratadine and minimal changes in 3-OH-desloratadine concentrations in patients with varying degrees of renal impairment. In a multiple-dose study, steady state was reached after Day 11, and compared to healthy subjects the exposure to desloratadine was ~1.5-fold greater in subjects with mild to moderate chronic renal insufficiency (CRI) and ~2.5-fold greater in subjects with severe CRI. In both studies, changes in exposure (AUC and C<sub>max</sub>) of desloratadine and 3-OH-desloratadine were not clinically relevant. Therefore, no dose adjustment is considered necessary, however, a warning concerning the use in patients with severe renal impairment is included in the SmPC (section 4.4).

For loratadine, the following text has been included in section 5.2 of the SmPC: 'In patients with chronic renal impairment, both the AUC and peak plasma levels (C<sub>max</sub>) increased for loratadine and its metabolite as compared to the AUCs and peak plasma levels (C<sub>max</sub>) of patients with normal renal function. The mean elimination half-lives of loratadine and its metabolites were not significantly different from that observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.'

For patients with severe liver impairment, a dose adjustment is recommended in the SmPC for loratadine as this population has reduced clearance of loratadine: 'an initial dose of 10 mg every other day is recommended for adults and children weighing more than 30 kg, and for children weighing 30 kg or less, 5 mg every other day is recommended.' In patients with chronic alcoholic liver disease, the AUC and C<sub>max</sub> of loratadine were double while the pharmacokinetic profile of desloratadine in the same study was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and desloratadine were 24 h and 37 h, respectively, and increased with increasing severity of liver disease.

For desloratadine, a dedicated Phase 1 study showed that a dose reduction is not recommended in patients with hepatic impairment, and no dose reduction nor any warning has been introduced in the product information.

In conclusion, while differences in pharmacokinetics of both substances have been observed, it has not been established that they would result in a significantly different safety profile between loratadine and desloratadine.

### **2.3.2. Therapeutic indications**

Currently, the originator desloratadine product (authorised for prescription-only use) is authorised in the European Union (EU) for the relief of symptoms associated with allergic rhinitis and urticaria.

In the majority of the EU Member States, loratadine has been widely available as an OTC-medicinal product indicated for the relief of symptoms associated with allergic rhinitis and chronic idiopathic urticaria. It is noted that chronic idiopathic urticaria is a more restricted indication than urticaria, one in which patients are more likely to be able to self-manage their condition.

### 2.3.3. Safety profile

Considering that desloratadine is the main metabolite of loratadine, the safety profiles of the two substances are not expected to be substantially different. However, it should be noted that a direct comparison between both substances is not possible due to the limitations of available clinical trial and spontaneous data.

The adverse reactions listed in the SmPCs of loratadine and desloratadine are compared in the table below:

**Table 1. Adverse reactions listed in section 4.8 of the summary of product characteristics (SmPC) of both desloratadine (DL) and loratadine (LOR). There may be differences in listed reactions between the SmPCs of different medicinal products with the same active substance.**

Adverse reactions from SmPC 4.8	DL	LOR
<b>Psychiatric disorders</b>		
Hallucinations	Very rare	-
Abnormal behaviour	Not known	-
Agression	Not known	-
<b>Nervous system disorders</b>		
Headache	Common	Common
Dizziness, somnolence, insomnia,	Very rare	Very rare (dizziness, convulsions) - common (somnolence) - uncommon (insomnia)
psychomotor hyperactivity, seizures	Very rare	-
<b>Cardiac disorders</b>		
Tachycardia, palpitations	Very rare	Very rare
QT prolongation	Not known	-
<b>Gastrointestinal disorders</b>		
Dry mouth	Common	Very rare (nausea, dry mouth, gastritis)
Abdominal pain, nausea, vomiting,	Very rare	-
dyspepsia, diarrhoea		
Increased appetite	-	Uncommon
<b>Hepatobiliary disorders</b>		
Elevations of liver enzymes,	Very rare	Very rare (abnormal hepatic function)
increased bilirubin, hepatitis		
Jaundice	Not known	-
<b>Skin and subcutaneous tissue disorders</b>		
Photosensitivity	Not known	-
Alopecia	-	Very rare
<b>Musculoskeletal and connective tissue disorders</b>		
Myalgia	Very rare	-
<b>General disorders and administration site conditions</b>		
Fatigue	Common	Very rare
Hypersensitivity reactions (such as	Very rare	Very rare (hypersensitivity reactions incl anaphylaxis, rash)
anaphylaxis, angioedema, dyspnoea, pruritus, rash, and urticaria)		
Asthenia	Not known	-
(-) signifies not listed		

A broader range of adverse reactions is listed for desloratadine than for loratadine (e.g. hallucinations, abnormal behaviour, aggression, psychomotor activity, QT prolongation, abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, jaundice, photosensitivity, myalgia and asthenia).

On the other hand, increased appetite (uncommon) and alopecia (very rare) are listed for loratadine but not for desloratadine. Furthermore, undesirable effects reported in the paediatric population for loratadine included headache (2.7%), being nervous (2.3%) and fatigue (1%). In the SmPC of desloratadine the following effects were listed for the paediatric population, not for loratadine: QT-prolongation, arrhythmia and bradycardia (all with unknown frequency).

The CHMP noted that the MAH for the originator medicinal product (Aerius) is currently conducting a post-authorisation safety study (PASS) to investigate whether there is an association between exposure to desloratadine and risk of seizure, supraventricular tachycardia, atrial fibrillation or flutter.

## **2.4. Expert consultation**

During the procedure, the CHMP consulted both the Safety Working Party (SWP) and the Pharmacovigilance Risk Assessment Committee (PRAC).

### **2.4.1. Safety Working Party**

The CHMP asked the Safety Working Party (SWP) to address two questions:

- 1. To what extent is the reported anti-muscarinic activity of desloratadine and its metabolites a plausible explanation for the possible clinical safety issues (including cardiac arrhythmias, QT changes, seizures, drowsiness, fatigue, dry mouth)?*

The SWP noted that following the therapeutic doses of desloratadine (5 mg QD) or loratadine (10 mg QD) a similar desloratadine plasma exposure (both C<sub>max</sub> and AUC) is reached suggesting similar (wanted and unwanted) effects related to desloratadine using therapeutic dosing of loratadine or desloratadine.

As desloratadine is a more potent (15 – 150-fold) histamine H<sub>1</sub>-receptor antagonist than loratadine and unbound desloratadine plasma levels are ~10-fold higher than for loratadine, it is likely that the clinical efficacy of both loratadine and desloratadine dosing may be largely related to the desloratadine exposure and its related metabolite(s).

The pharmacokinetics of desloratadine in humans is linear with dose and not or minimally influenced by food, race, gender, age or drug interaction but a poor metaboliser phenotype (4-6% frequency) has an increased C<sub>max</sub> (3-fold) and AUC (6-fold). Further clinical studies showed that this phenotype was not associated with higher adverse event reporting.

The above mentioned clinical safety issues such as cardiac arrhythmias, seizures, drowsiness, fatigue and dry mouth are known side effects of anti-muscarinic agents. Across the five subtypes of muscarinic receptors desloratadine demonstrated receptor affinities ranging from 20-50 nM<sup>4</sup>, whereas loratadine demonstrated weaker affinity for the muscarinic receptors in the range of 2,000-10,000 nM. Preclinical studies showed desloratadine to be a potent and selective human histamine H<sub>1</sub>-receptor antagonist (K<sub>i</sub> 0.4 – 0.9 nM) with relatively low affinities for muscarinic receptors (K<sub>i</sub> values of 50, 47, 125, 104 and 320 nM at the human muscarinic M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub> and M<sub>5</sub> receptors, respectively) and histamine H<sub>2</sub> (K<sub>i</sub>

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<sup>4</sup> Aerius: EPAR - Scientific discussion. Available from URL: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Scientific\\_Discussion/human/000313/WC500022748.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000313/WC500022748.pdf)



value of 353 nM)<sup>5,6</sup>. Gillard et al.<sup>7</sup> found the selectivity ratio of H1 receptor versus the muscarinic receptors for loratadine to be 100 - 500 and for desloratadine 50 - 125, making desloratadine, having the lowest ratio of the six investigated anti-histamines, the most likely compound to induce muscarinic side-effects based on these in vitro receptor affinities. Preclinical in vivo studies confirmed the M2 and M3 anti-muscarinic activities of desloratadine but at exposure levels unlikely to be reached following normal therapeutic doses<sup>8</sup>. A wide range of polymorphisms have been reported in muscarinic receptor genes but no conclusions can be drawn on a possible clinical role as studies linking the polymorphisms to phenotypes or to the impact of drug responsiveness are largely missing<sup>9</sup>.

Therefore, given the 50 – 125 fold selectivity in affinity of histamine H1 over the muscarinic receptors and the fact that, when dosing 5 mg desloratadine, the human clinical therapeutic dose, maximal plasma (C<sub>max</sub>) desloratadine was ~10 nM (total i.e. ~2 nM unbound), a very low risk for anti-muscarinic related safety issues is anticipated.

A role of competitive binding by loratadine on histamine/muscarinic receptors has been suggested, potentially decreasing the apparent activity of desloratadine. This is not expected as ~100-fold more loratadine is needed to compete with desloratadine for the H1-receptor<sup>10</sup>. A similar conclusion can be expected for such a competition with the muscarinic receptors given the much lower binding affinity of loratadine (Gillard et al, 2003).

Regarding possible central effects of desloratadine, various primate and non-primate models did not indicate a penetration of the normal physiologically intact blood-brain barrier<sup>8, 11</sup>.

3-OH-desloratadine, the metabolite of desloratadine, is present in human plasma at similar exposure (C<sub>max</sub>, AUC, T<sub>1/2</sub><sup>12</sup>) as desloratadine (upon desloratadine as well as loratadine dosing). This compound is denoted as an active metabolite as it has a comparable antagonistic activity on the histamine H1-receptor and a possible role of 3-OH-desloratadine on the raised clinical safety issues can not be excluded but no information could currently be found related to possible anti-muscarinic activity.

Concerning a potential to QTc changes, it has been shown that desloratadine does not interfere with HERG channels (up to 10 µM) nor on cardiac conduction parameters in preclinical in vivo studies and in humans a 9-fold higher than therapeutic desloratadine dose (45 mg QD, 10 days) did not result in clinically relevant ECG changes. These results point towards a very low risk of ventricular arrhythmia by desloratadine (Henz, 2001). Since then, a stronger pro-arrhythmic potential was found with five anti-histamines including desloratadine and loratadine but a PRAC assessment concluded that there were signals of disproportional reporting (SDR) for QT prolongation for all concerned anti-histamines but for TdP only for cetirizine and loratadine. Overall, the number of supportive cases for any of the substances was considered low.

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<sup>5</sup> Handley DA, McCullough JR, Fang Y, Wright SE, Smith ER. (1997) Descarboethoxyloratadine, a metabolite of loratadine, is a superior antihistamine. *Ann Allergy Asthma Immunol* 78: P164

<sup>6</sup> Kreutner W et al. (2000) Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H1 receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergenic effects. *Arzneimittelforschung*. 50(4):345-52

<sup>7</sup> Gillard M et al. (2003) H1 antagonists: receptor affinity versus selectivity. *Inflamm Res*;52(1):S49-S50

<sup>8</sup> Howel G et al. (2005) *In vivo* antimuscarinic actions of the third generation antihistaminergic agent, desloratadine. *BMC Pharmacology* 5: 13

<sup>9</sup> Michel JC, Teitsma CA. (2012) Polymorphisms in human muscarinic receptor subtype genes. *Handb Exp Pharmacol*. 208: 49-59

<sup>10</sup> Anthes JC et al. (2002) Biochemical characterization of desloratadine, a potent antagonist of the human histamine H1 receptor. *Eur J Pharm* 449: 229–237

<sup>11</sup> Henz BM. (2001) The pharmacologic profile of desloratadine: a review. *Allergy* 56: 7-13

<sup>12</sup> Xu et al. (2007) Simultaneous determination of desloratadine and its active metabolite 3-hydroxydesloratadine in human plasma by LC/MS/MS and its application to pharmacokinetics and bioequivalence. *J Pharm Biomed Anal*. 30; 45(4):659-66

Therefore, having considered this question in detail, the SWP concluded that the possible clinical safety issues, such as cardiac arrhythmias, drowsiness, fatigue and dry mouth, may be related to anti-muscarinic activity of desloratadine but this risk is considered very low at the therapeutic doses given its receptor selectivity and unbound plasma levels.

This is in line with results from post-marketing surveillance studies in 77,880 subjects (0.37% AEs) where the most commonly reported AE related to treatment were fatigue (0.07%), headache (0.07%), dry mouth (0.04%) and nausea (0.03%).

The SWP also noted that there is a lack of data on the anti-muscarinic activity of a major metabolite, 3-OH-desloratadine, and its potential role in these clinical safety issues. However, given that the levels of this metabolite are similar following administration of desloratadine and loratadine, it is unlikely that this would translate to a difference in safety between desloratadine and loratadine.

- 2. Are there non-clinical data suggesting that the safety profiles of desloratadine and loratadine are different, in doses equivalent to standard proposed clinical doses and equivalent to higher doses (up to 4 times the standard proposed clinical doses)?*

The SWP noted that non-clinical studies conducted with desloratadine and loratadine demonstrated that there are no qualitative or quantitative differences in the toxicity profile of desloratadine and loratadine (at comparable levels of exposure to desloratadine).

In the rat repeated dose toxicity study, the no-effect dose was 3 mg/kg, which was associated with a 30-fold higher desloratadine AUC than in humans. In monkeys, doses up to 12 mg/kg (182-fold higher AUC) were generally well tolerated. The no-effect dose is 6 mg/kg.

As in humans, also in animals loratadine is quickly converted to desloratadine making it difficult to discriminate between the two compounds in in vivo studies. In addition, in animals desloratadine metabolism is different (more 5- and 6-hydroxylation as compared to 3-hydroxylation in man) as compared to humans. Further in vitro and ex vivo studies comparing the two compounds have been reported in literature but mainly in relation to histamine and muscarinic antagonism and HERG channel function or related to allergic inflammation processes and no new safety issues have been identified.

The SWP therefore concluded that, given the currently available (pre)clinical pharmacodynamic and pharmacokinetic information, a similar safety profile is to be anticipated with daily administration at standard proposed clinical doses (5 mg desloratadine or 10 mg loratadine) or at doses 4-fold higher.

#### **2.4.2. Pharmacovigilance Risk Assessment Committee**

The CHMP asked PRAC to provide its advice on two specific aspects. The responses to the questions put forward by CHMP were provided on the basis of PRAC's knowledge of the safety profile of desloratadine, and in particular of data arising from spontaneous reporting.

The Pharmacovigilance Risk Assessment Committee (PRAC) noted that desloratadine was first authorised in the EU in 2001. The originator is centrally authorised and there are also a number of marketing authorisations in the EU for nationally approved products, some of which are already available as OTC. For the originator, worldwide cumulative patient exposure up to 30 June 2016 is estimated to be 32 375 751 patient-years of treatment<sup>13</sup>.

When asked to consider whether the safety profile of desloratadine was sufficiently described by CHMP in its preliminary report and whether there are additional safety data to be taken into consideration

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<sup>13</sup> PRAC AR for Desloratadine PSUSA (EMA/H/C/PSUSA/00000962/201607), adopted by PRAC in March 2017

before a scientific recommendation can be made on the prescription status, PRAC noted the recent addition to the SmPC of desloratadine of the adverse reactions 'abnormal behaviour' and 'aggression' with a frequency unknown, and of a warning regarding convulsions. PRAC also highlighted that nationally authorised products have recently been asked to align its SmPC with that of the originator by adding the adverse reaction 'QT prolongation' and pointed to additional publications on this topic<sup>14,15</sup>. In addition, PRAC noted that MAHs of the centrally authorised medicinal products containing desloratadine were requested to provide an analysis of all available data regarding movement disorders (including dystonia, tics and extrapyramidal symptoms) and discuss whether 'movement disorders' should be included in the SmPC as an adverse reaction. The assessment of this analysis is not yet available.

When asked to what extent (if any) does PRAC consider the overall safety profile of desloratadine different from that of loratadine, also in view of the ongoing category 3 PASS, PRAC generally agreed with the SWP's conclusion that the safety profile of desloratadine is expected to be similar to that of loratadine at standard clinical doses. However, PRAC noted that a direct comparison between the safety profiles of desloratadine and loratadine is not possible due to the inherent limitations of clinical trials and of spontaneous data. Data sets for the products are different due to the different indications and patient exposures (much larger exposure for loratadine than for desloratadine), and the possible differences in adverse drug reaction reporting between a POM product and an OTC product.

The ongoing PASS study for desloratadine is expected to examine the association between desloratadine and the risks of seizure, supraventricular tachycardia and atrial fibrillation or flutter. The study may provide reassurance on these risks and enable to stratify results per age and concomitant patient condition or other factors affecting the onset of these clinical events. At present, PRAC considered that the available information does not justify any changes to the risk management activities of desloratadine-containing products.

In conclusion, based on currently available information, PRAC considered that it is not possible to perform a direct comparison between the safety profiles of desloratadine and loratadine. It was noted that the SmPCs differ between the two active substances, but the inherent limitations of clinical trials and spontaneous reporting data preclude firm conclusions in this regard. PRAC will continue to regularly monitor the safety profile of both desloratadine and loratadine. The ongoing PASS is expected to clarify existing uncertainties in the safety profile of desloratadine. Based on the information currently available, it is not possible to draw a conclusion on whether differences in prescription status impact the risk associated with each product.

## **2.5. Overall discussion and conclusion**

Having considered the currently available data on desloratadine, as well as the input from both the SWP and the PRAC, the CHMP considered whether desloratadine-containing products could be switched from 'medicinal products subject to prescription' to 'medicinal products not subject to prescription'.

The CHMP noted that desloratadine is the primary active metabolite of loratadine, and following administration of therapeutic doses of both compounds a similar desloratadine plasma exposure (both C<sub>max</sub> and AUC) is reached suggesting similar clinical effects.

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<sup>14</sup> Torsade De Pointes and QT Prolongation Could Result From Desloratadine Anti-Allergy Treatment. Ali AK. Value Health. 2015 Nov; 18(7):A493-4.

<sup>15</sup> Pro-arrhythmic risk of oral antihistamines (H1): Combining adverse event reports data with drug utilization data across Europe. Godman B, Poluzzi E, Raschi E, Koci A, Kalaba M, Wettermark B. et al. Basic Clin Pharmacol Toxicol. 2014; 115(1):83.

The CHMP recognises that there are apparent differences in the safety profiles of loratadine and desloratadine as described in product information for both compounds. However, a direct comparison between the safety profiles of loratadine and desloratadine is not possible on this basis, due to the limitations of clinical trials and of spontaneous data. Data sets for the products are different due to different indications, different patient exposure and possible differences in adverse reaction reporting between products with prescription and non-prescription status.

It is also acknowledged that there is an ongoing PASS study which is expected to clarify existing uncertainties in the safety profile of desloratadine. However, results will not be immediately available and based on current knowledge of both substances, the safety profile of desloratadine is not expected to significantly differ from that of loratadine at standard clinical doses.

Therefore the CHMP concluded that, when administered at standard clinical doses according to the terms of the marketing authorisations, the safety profile and clinical effects of desloratadine are expected to be similar to those of loratadine, which is already widely available in the EU as a non-prescription medicinal product. Provided relevant aspects of a potential switch are assessed and considered by the competent authorities by analogy to loratadine, the CHMP considers that a change of legal status for desloratadine-containing products may be acceptable.

## Appendix 1

### *Divergent position(s)*

## Article 5(3) of Regulation (EC) No 726/2004

Desloratadine-containing medicinal products

Procedure no: EMEA/H/A-5(3)/1431

### Divergent statement

The CHMP assessment report makes a recommendation based on the fact that it is not expected that the clinical effects of desloratadine would substantially differ from those of loratadine, which is already widely available in the European Union (EU) as a non-prescription medicinal product.

However, we argue that it is currently not acceptable to extrapolate the non-prescription status of loratadine to desloratadine. Indeed, we consider it necessary to assess the criteria for classifying a medicinal product as subject to a medical prescription or not as presented in the European Commission's (EC) 'guideline on changing the classification for the supply of a medicinal product for human use' (Rev. Jan 2006) specifically for desloratadine.

In this context, as some of the criteria listed in this guideline are considered not fulfilled, we are of the opinion that an "over-the-counter" (OTC)-switch for desloratadine is not appropriate at this stage.

Indeed, the first criterion of this EC's Switch guideline is considered **not fulfilled** for OTC-switch in adults/adolescents/children for desloratadine due to:

- the **uncertainties about the safety profile** of desloratadine in the prescription-only-medicine (POM)-setting at this stage, i.e. :
  - risks of supraventricular arrhythmia, atrial fibrillation, atrial flutter and first seizure/first recurrence of seizure for which the **PRAC advice** states that the ongoing **post authorisation safety study (PASS)** is expected to clarify existing uncertainties in the safety profile of desloratadine and to give information to *stratify the risk*. This may permit to propose possible *risk minimization measures* if deemed required;
  - risk of movement disorders (including dystonia, tics and extrapyramidal symptoms) for which a **legally binding measure (LEG)** has been requested in the recent PSUSA procedure;
- the fact that the **risk of QT prolongation** is listed in section 4.8 of the SmPC of desloratadine. This was added to provide information for prescribing physicians to assist in evaluating the risk/benefit of desloratadine treatment in patients with known arrhythmias or with concomitant treatment known to prolong the QTc interval. Moreover, a recent WHO analysis concluded that the reports in Vigibase® might possibly indicate that desloratadine contributes to QT prolongation when interacting with other drugs with QT prolonging potential or when possible confounders are present. Furthermore, the recent PSUSA procedure still considers QTc interval prolongation as an important potential risk in the summary of safety concerns and the MAH is asked to closely monitor the risk. Information on concomitant drugs that could potentiate these adverse events by affecting the pharmacokinetics of desloratadine (like e.g. montelukast) or information on concomitant administration of drugs that could impact the QT interval, is still not available to be included in the SmPC. Risk of QT prolongation is an **important safety concern** to be considered in the context of a

**potential OTC-switch**; it is a listed adverse reaction for desloratadine, not for loratadine. Patients at risk are not easily identifiable by the pharmacist, nor is the risk of QT-prolongation easily manageable by the pharmacist or by the patient with cardiac risk factors himself in an OTC-context.

In addition, the third criterion of the EC's Switch guideline is considered **not fulfilled** for OTC-switch as further investigation is **required and ongoing**:

The **PASS** will provide important information on the safety profile of desloratadine. If, in the future, safety concerns (i.e. seizure or arrhythmias) are confirmed for desloratadine, it would be difficult to justify today's opinion in favor of an OTC-status for desloratadine in view of the current uncertainties. Moreover, as confirmed in the PRAC advice, information from the PASS is required to *stratify the risk* e.g. in elderly and patients with concomitant conditions or other factors affecting the onset of these clinical events. This may permit to propose possible *risk minimization measures*.

Within a **LEG-procedure**, as an outcome of the recent PSUSA procedure, a further analysis of all available data regarding movement disorders (including dystonia, tics and extrapyramidal symptoms) has been requested.

These analyses should be awaited before increasing exposure through an OTC-switch may be considered.

**CHMP members expressing a divergent opinion:**

Andrea Laslop (AT)	22 June 2017	Signature: .....
Bart Van der Schueren (BE)	22 June 2017	Signature: .....
Daniela Melchiorri (IT)	22 June 2017	Signature: .....
Jacqueline Genoux-Hames (LU)	22 June 2017	Signature: .....
Koenraad Norga (co-opted)	22 June 2017	Signature: .....
Jean-Louis Robert (co-opted)	22 June 2017	Signature: .....