15 October 2020
EMA/592592/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Desloratadine ratiopharm

International non-proprietary name: desloratadine

Procedure No. EMEA/H/C/002404/II/0023/G

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Jan 2020	27 Jan 2020	☐
☐	CHMP Rapporteur Assessment Report	25 Feb 2020	25 Feb 2020	☐
☐	PRAC Rapporteur Assessment Report	28 Feb 2020	25 Feb 2020	☐
☐	PRAC members comments	04 Mar 2020	04 Mar 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Mar 2020	05 Mar 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	12 Mar 2020	12 Mar 2020	☐
☐	CHMP members comments	16 Mar 2020	16 Mar 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Mar 2020	19 Mar 2020	☐
☐	Request for supplementary information	26 Mar 2020	26 Mar 2020	☐
☐	Submission of MAH responses	20 May 2020	27 May 2020	☐
☐	Re-start of procedure	25 May 2020	25 May 2020	☐
☐	CHMP Rapporteur Assessment Report	23 June 2020	22 June 2020	☐
☐	PRAC Rapporteur Assessment Report	26 June 2020	22 June 2020	☐
☐	PRAC members comments	01 July 2020	01 July 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	02 July 2020	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	09 July 2020	09 July 2020	☐
☐	CHMP members comments	13 July 2020	13 July 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	16 July 2020	17 July 2020	☐
☐	Request for supplementary information	23 July 2020	23 July 2020	☐
☐	Submission of MAH responses	15 Sept 2020	15 Sept 2020	☐
☐	Re-start of procedure	16 Sept 2020	16 Sept 2020	☐
☐	CHMP Rapporteur Assessment Report	30 Sept 2020	30 Sept 2020	☐
☐	CHMP members comments	05 Oct 2020	05 Oct 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Oct 2020	09 Oct 2020	☐
☒	Opinion	15 Oct 2020	15 Oct 2020	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, ratiopharm GmbH submitted to the European Medicines Agency on 9 January 2020 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal product for centrally authorised products - All other legal status changes	Type II	I, II, IIIA and IIIB
C.I.6.b	C.I.6.b - Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication	Type IB	I, IIIB

C.I.5.b - Change in the legal status of desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of desloratadine ratiopharm and the post-marketing experience already available with other medicinal products containing similar long acting histamine antagonists. The RMP version 1.0 has also been submitted. In addition, the MAH also took the opportunity to bring the PI in line with the latest QRD template (version 10.1), to update the list of local representatives in the package leaflet and to make editorial changes.

C.I.6.b - To delete the therapeutic indication in adolescents aged 12 years and older for the relief of symptoms associated with allergic rhinitis and urticaria. Section 4.1 of the SmPC and section 1 of the PL are updated accordingly.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex IV and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Desloratadine ratiopharm 5 mg film-coated tablets is a generic medicinal product approved in the European Union (EU) on 13 January 2012 in adults and adolescents aged 12 years and older for the relief of symptoms associated with allergic rhinitis and urticaria. The reference medicinal product is Aerius authorised in the EU on 15 January 2001.

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H1-receptor antagonist activity. Desloratadine is the primary active metabolite of loratadine, which has been available in a number of Member States as an 'non-prescription' medicinal product for many years.

In the present application, the MAH ratiopharm GmbH proposes to change the legal status of Desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Desloratadine ratiopharm and the post-marketing experience already available with other medicinal products containing similar long acting histamine antagonists. In addition, the MAH proposes to delete the therapeutic indication in adolescents aged 12 years and older as according to the current available data and referent medicinal product, they believe the change of legal status in this population would not be supported by a positive benefit-risk in view of the limited clinical trial data in this population and the adverse drug reactions like seizures reported in the paediatric population. QT prolongation, arrhythmia, bradycardia, abnormal behaviour, and aggression were also reported in post-marketing in paediatric population. Considering these safety and

efficacy aspects, the MAH decided that it is more appropriate to approve desloratadine as non-prescription medicine only for adults.

In support of this request, the MAH provided a clinical overview including a comprehensive analysis based on literature data and pharmacovigilance database, as well as a justification for fulfilment of the criteria to change of medical prescription status as stated in the European Commission 'Guideline on changing the classification for the supply of a medicinal product for human use' (Revision January 2006). Furthermore, rationale is provided to support that the CHMP 'Guideline on legal status for the supply to the patient of centrally authorised medicinal products' (EMEA/186279/2006) for classifying the product as subject to medical prescription no longer applies to Desloratadine ratiopharm[1,2].

A revised product information has been submitted together with a risk management plan (RMP).

The submitted data and the four criteria mentioned in Article 71 of Directive 2001/83/EC and the European Commission Guideline on changing the classification for the supply of a medicinal product for human use have been considered by the CHMP during the assessment of the variation.

CHMP also took note of the referral under Article 5(3) of Regulation (EC) No 726/2004 on desloratadine-containing medicinal products (EMA/421768/2017) from 2017 which reviewed the prescription status of desloratadine containing medicinal products and concluded that, provided that all relevant aspects of a potential switch are assessed and considered by the competent authorities by analogy to loratadine, a change of legal status for desloratadine-containing products may be acceptable[3]. However, CHMP acknowledged that existing uncertainties in the safety profile of desloratadine were expected to be clarified with a post-authorisation safety study (PASS) that was ongoing and is now completed. Nonetheless these uncertainties were not expected to significantly differ from that of loratadine at standard clinical doses.

The following criteria for classifying Desloratadine ratiopharm as medicinal non subject to medical prescription were thus assessed:

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision.

(1.1.) Direct danger/safety profile

In (pre)clinical studies and post-marketing experience, desloratadine has shown a good safety profile with only a low incidence of mild-to-moderate drug related side effects. The MAH performed a comprehensive analysis based on literature data and Teva pharmacovigilance database.

No new information has become available regarding the toxicity profile of desloratadine and it is considered that desloratadine has a low general toxicity and no relevant productive toxicity, genotoxic or carcinogenic properties. The pre-clinical section of the summary of product characteristics (SmPC) is considered up to date and no changes are proposed in this variation, which is agreed by CHMP.

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of desloratadine during pregnancy. The product information is considered up-to-date and

[1] EC guideline 'Guideline on changing the classification for the supply of a medicinal product for human use' (Revision January 2006)
[2] CHMP guideline 'Guideline on legal status for the supply to the patient of centrally authorised medicinal products' (EMEA/186279/2006)
[3] Desloratadine-containing medicinal products. Assessment report. Article 5(3) of Regulation (EC) No 726/2004. EMA website: https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-desloratadine-containing-medicinal-products_en.pdf

no changes are proposed regarding pregnancy in this variation, which is agreed by CHMP. With regard to breast-feeding, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from desloratadine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. The section 4.6 of the SmPC is updated to state that breast-feeding women shall seek medical advice before using desloratadine. Use in lactation is also listed as a missing information in the summary of safety concerns in the RMP. The section 2 of the package leaflet is updated accordingly.

In the Article 5(3) referral procedure, CHMP concluded that, when administered at standard clinical doses according to the terms of the market 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. The uncertainties discussed during the referral about the direct danger regarding supraventricular tachycardia (SVT), atrial fibrillation and atrial flutter, seizures as well as regarding movement disorders have since then been assessed by PRAC in a Nordic register-based study (PASS - EUPAS15038) (procedure numbers: MEA 065; EMEA/H/C/WS1655) and a post-authorisation measure for movement disorders (procedure number: LEG 006).

In the PASS study, no association between current use of desloratadine and risk of first SVT was found. No regulatory actions were considered necessary, also taking into account limited evidence from spontaneous reporting. Further monitoring is to be performed by means of routine pharmacovigilance and SVT should be listed as an important potential risk in the summary of the safety concerns in the RMP. No causal association could be drawn with regard to atrial fibrillation or flutter in the study however the MAH was requested to further investigate this risk and provide a review in the next PSUR (due in 2021). The study also indicated an increased incidence of new-onset seizure in patients 0 to 19 years of age when receiving desloratadine compared with periods not receiving desloratadine. The section 4.8 of the SmPC of the reference product Aerius was therefore updated to reflect the increased incidence of new-onset seizure in patients 0 to 19 years of age receiving desloratadine compared with periods not receiving desloratadine. No association was found of first seizure and desloratadine use in patients aged above 20 years. Although the paediatric indication is deleted as part of this variation, the section 4.8 of the SmPC should be updated in accordance with the reference product to reflect the current safety knowledge in this younger population (see also section 6.).

A review of the available evidence carried out by the MAH is also not suggestive of an association between desloratadine use and the occurrence of movement disorders (see also section 6.).

Abnormal hepatic function was reported in 8 adult patients from the comprehensive review carried out by the MAH. All cases are confounded by other factors; therefore, a direct causality between desloratadine and the hepatic effects cannot be determined. However, elevations of liver enzymes, increased bilirubin, hepatitis are listed as very rare events with jaundice unknown. Therefore, in the case of severe hepatic impairment, desloratadine should be used with caution, as hepatitis and jaundice are possible adverse reactions. A warning in section 4.4 of the SmPC is included about this risk in this variation (see also section 6.). The section 4.8 of the SmPC and section 4 (possible side effects) of the package leaflet already include the adverse reactions elevations of liver enzymes, increase bilirubin, hepatitis (liver inflammation and abnormal liver function tests) with a frequency very rare and jaundice (yellowing of the skin and/or eyes) with a frequency not known.

There are no known interactions with commonly used medicines.

Based on the safety profile, CHMP considered that Desloratadine ratiopharm is not likely to present a direct danger when used correctly, without medical supervision, in the adult population.

(1.2) Indirect danger/safety profile

With regard to the absence of indirect danger, CHMP agrees that the risk of masking and or hiding underlying conditions is highly unlikely when it is used in the authorised conditions. Allergic rhinitis is a self-limiting disease, and for a first episode of allergic rhinitis, it is most likely that a patient will have sought a physician for appropriate treatment. For a next episode of allergic rhinitis, symptoms are known and patients already know their disease and they can self-manage their disease. For chronic idiopathic urticaria, it is specifically mentioned it needs to be diagnosed initially by a physician, which limits the indirect danger for non-prescription use. The product information advises patients to seek medical advice if symptoms persist for more than 7 days or deteriorate in order to minimise the risk of masking an underlying disease. There is no risk of increased resistance to desloratadine, based on currently available pharmacokinetic data, clinical trials and post-marketing data.

(1.3) Self-assessment

CHMP considered the allergic rhinitis can be easily assessed by adult patients, due to the symptomatology which is recognisable and manifests when the patient is exposed to a certain allergen. Furthermore, allergic rhinitis itself is not life-threatening (unless accompanied by severe asthma or anaphylaxis) and the package leaflet (PL) provides adequate description of the allergic rhinitis symptoms.

With regard to the indication of urticaria, CHMP acknowledges that the condition may be confused with a variety of other dermatologic disease, as it can be similar in appearance and pruritic, such as atopic dermatitis (eczema), maculopapular drug eruptions and others. This is in particular applicable to acute urticaria which may wrongly be assessed by the patient if never diagnosed with the condition and may also delay the diagnosis. For chronic urticaria, the patient should have been diagnosed by a physician and should be able to recognise the symptoms. Therefore, taking into account the risk of misdiagnosis or progression to a life-threatening angioedema and/or anaphylactic shock (as well as no extensive non-prescription medicine experience exists with desloratadine nor loratadine in the acute urticaria indication), CHMP considers that the urticaria indication should be restricted from 'urticaria' to 'chronic idiopathic urticaria as initially diagnosed by a physician' for the product to be used in a non-prescription setting. In addition, a warning in section 4.4 of the SmPC is added to state that chronic idiopathic urticarial should initially by diagnosed by a physician. In case of symptom that indicate angioedema, the patient needs to seek medical help immediately. The package leaflet is updated accordingly with the corresponding warnings.

Both indications (allergic rhinitis and chronic idiopathic urticaria) have already been accepted as non-prescription-indication for other medicinal products. It is considered that the vast majority of the targeted patients can properly assess their symptoms without medical supervision. This is even more likely considering the indication has been limited to adults only. Appropriate information about the description of the symptoms are included in the package leaflet. Patients are also advised to consult their doctor or pharmacist, if they need advice.

(1.4) Risk and consequences of incorrect use

Risk and consequences of incorrect use are considered low and can be effectively mitigated by the information in the PL, SmPC and labelling. The listed medical conditions as contraindications, precautions and warnings are chronic disease and are chronically supervised. These chronic patients will also know their status which limits incorrect use. Clear instructions on symptomatology and posology, as well as instructions on when to seek additional advice from a physician are present in the patient leaflet.

(1.5) Patient information

The written information (PL and labelling) has been updated and the CHMP considered that the changes were adequate to contribute effectively to safe and effective use of the medicine. Contra-indications, interactions, warning and precautions are few and can be readily understood in lay language.

In view of the current safety profile of desloratadine containing medicinal products, it is unlikely that Desloratadine ratiopharm will present a danger either directly or indirectly if utilised without medical supervision in the adult targeted population. This is also supported by the current safety knowledge on other similar products available as non-prescription medicines in some EU countries. CHMP concluded that criterion 1 does not apply to Desloratadine ratiopharm.

2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

Known incorrect use is low and does not pose a direct or indirect danger to human health. Cases of alcohol intolerance and intoxication have been reported during post-marketing use. Although this risk is considered low, appropriate information about the risk of interaction with alcohol is already included in the SmPC and PL. In addition, considering the available data of misuse, abuse and overdose it is concluded that the health consequences for the patients in case of misuse, overdose, increased dose, abuse are mild and limited (see section 6.).

Therefore, CHMP considered that Desloratadine ratiopharm is unlikely to be frequently and to a very wide extent used incorrectly in a non-prescription setting, and as a result is unlikely to present a direct or indirect danger to human health. CHMP concluded that criterion 2 does not apply to Desloratadine ratiopharm.

3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation.

(3.1) Recent authorisation/ limited experience

With regard to the recent authorisation/ limited experience criterion, CHMP agrees that patient experience with desloratadine is widespread, both as prescription and non-prescription medicines allowing for a good characterisation of the safety profile. Desloratadine ratiopharm product has been on the market since 2012, while the reference product Aerius has its marketing authorisation since 2001; hence, there is a long experience on the market. The MAH markets non-prescription desloratadine in Bulgaria, Finland, Poland, Sweden, while other MAHs have also non-prescription sales in Hungary and Denmark.

In addition, as mentioned above, a non-interventional non-imposed PASS was conducted to assess the potential risk of desloratadine exposure on seizures, SVT, and atrial fibrillation or flutter, as well as a post-authorisation measure concerning movement disorders (see section 6.). Appropriate safety information was included in the product information following review of the mentioned data.

(3.2) New strength, dose, route of administration, indication, new age group or combination of substances

With this variation the MAH does not apply for a new strength, dose or route of administration. However, as a consequence of the change of legal status, the urticaria indication and age group are restricted to chronic urticaria and adults only, as mentioned above.

Overall, CHMP concluded that criterion 3 does not apply.

4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

Desloratadine ratiopharm is for oral use and therefore not to be administered parentally (for injection). The fourth criterion does not apply.

5. Other considerations: supply not subject to medical prescription

Considering that seasonal allergic rhinitis can last for 6 weeks to even 3 months, it is considered

necessary to limit pack size to 30 tablets. Therefore, the pack sizes of 40, 50, 60, 90 and 100 tables are deleted (EU/1/11/746/007-011).

The outer packaging as well as the patient information contains clear and precise recommendations. This has been confirmed in the Readability Testing.

In conclusion, the CHMP considered that the criteria mentioned in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use do not apply to Desloratadine ratiopharm and therefore the change from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription" is approvable.

CHMP also agreed with the MAH to restrict the indications for Desloratadine ratiopharm to adults only as the paediatric population would not be compatible with the proposed change of legal status. The adverse drug reactions reported in the post-marketing setting in this young population (seizures, QT prolongation, arrhythmia, bradycardia, abnormal behaviour, and aggression) do not support the use of this product without a medical prescription in the paediatric population.

CHMP also took into account that there are other desloratadine containing medicinal products authorised in the adolescents and acute urticaria indications that can be used with medical prescription.

Therefore, the following indications are acceptable:

Desloratadine ratiopharm is indicated in adults for the relief of symptoms associated with:

- *allergic rhinitis (see section 5.1)*
- *chronic idiopathic urticaria as initially diagnosed by a physician (see section 5.1)*.

The SmPC, labelling, Annex II, PL are updated accordingly. In addition, the product information is updated in line with the latest QRD template (version 10.1).

The benefit-risk balance of Desloratadine ratiopharm remains unchanged.

With this variation, a risk management plan (RMP) has been created and the final agreed version is version 1.2.

Furthermore, the Committee considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

This variation changes the legal status of the medicinal product, as discussed in section 3 below.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations approved		**Type**	**Annexes affected**
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal product for centrally authorised products - All other legal status changes	Type II	I, II, IIIA and IIIB
C.I.6.b	C.I.6.b - Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication	Type IB	I, IIIB

C.I.5.b - Change in the legal status of desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription'. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC are updated. The annex II, package leaflet and labelling are updated accordingly. Furthermore, the product information is brought in line with the latest QRD template (version 10.1) and the list of local representatives in the package leaflet is updated. The RMP is updated to version 1.2. As a consequence of the variation, the pack sizes of 40, 50, 60, 90 and 100 tablets are deleted (EU/1/11/746/007-011).

C.I.6.b - To delete the therapeutic indication in adolescents aged 12 years and older for the relief of symptoms associated with allergic rhinitis and urticaria. Section 4.1 of the SmPC and section 1 of the PL are updated accordingly.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II, IIIA, IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Desloratadine ratiopharm H-C-2404-II-23-G'

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Desloratadine ratiopharm 5 mg film-coated tablets was approved in the European Union (EU) on 13 January 2012 in adults and adolescents aged 12 years and older for the relief of symptoms associated with: allergic rhinitis and urticaria.

Desloratadine ratiopharm is a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC to the reference product Aerius which was authorised in the EU on 15 January 2001.

The active substance desloratadine is a non-sedating, long-acting histamine antagonist with 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 'non-prescription' medicinal product for a number of years.

In the present application, the MAH ratiopharm GmbH proposes to change the legal status of desloratadine ratiopharm from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in view of the safety profile of Desloratadine ratiopharm and the post-marketing experience already available with other medicinal products containing similar long acting histamine antagonists.

In addition, the MAH proposes to delete the therapeutic indication in adolescents aged 12 years and older as according to the current available data and referent medicinal product, they believe the change of legal status in this population would not be supported by a positive benefit risk in view of the limited clinical trial data in this population and the adverse drug reactions like seizures reported in the paediatric population. QT prolongation, arrhythmia, bradycardia, abnormal behaviour, and aggression were also reported in post-marketing in paediatric population. Considering these safety and efficacy aspects, the MAH decided that it is more appropriate to approve desloratadine as non-prescription medicine only for adults.

A revised product information has been submitted together with a risk management plan (RMP).

The MAH submitted a clinical safety analysis based on literature data and pharmacovigilance database, and the reason why they consider the criteria for classifying Desloratadine ratiopharm as subject to a medical prescription no longer apply.

In this variation, CHMP also took note of the referral under Article 5(3) of Regulation (EC) No 726/2004 on desloratadine-containing medicinal products (EMA/421768/2017) from 2017 which reviewed the prescription status of desloratadine containing medicinal products and concluded that, provided that all relevant aspects of a potential switch are assessed and considered by the competent authorities by analogy to loratadine, a change of legal status for desloratadine-containing products may be acceptable. However, CHMP acknowledged that existing uncertainties in the safety profile of desloratadine were expected to be clarified with a PASS that was ongoing and is now completed. Nonetheless these uncertainties were not expected to significantly differ from that of loratadine at standard clinical doses[3].

6. Clinical Safety aspects

Summary of safety profile

In clinical trials in a range of indications including allergic rhinitis and chronic idiopathic urticaria, at the recommended dose of 5 mg daily, undesirable effects with desloratadine were reported in 3 % of patients in excess of those treated with placebo. The most frequent of adverse reactions reported in excess of placebo were fatigue (1.2 %), dry mouth (0.8 %) and headache (0.6 %). The tabulated list of adverse reactions (ADR) can be found in section 4.8 of the SmPC.

The worldwide exposure of Teva desloratadine 5 mg tablets (until 31 January 2019) was 1.247.742.307 patient-days or 41.591.410 patient-months. This equates 3,465, 950.833 years.

The EU exposure for the same cumulative period was 916.389.074 patient-days, and 30.546.302 patient-months or 2,545,525.166 years.

Teva markets non-prescription desloratadine in Bulgaria, Finland, Poland, Sweden, while other MAHs have also non-prescription sales in Hungary and Denmark.

The MAH performed a comprehensive analysis based on literature data and Teva pharmacovigilance database by taking into account previous safety discussions within the latest periodic safety update report (PSUR) covering the period 16 July 2011 to 15 July 2016 (EMEA/H/C/PSUSA/00000962/201607 dated March 2017). The pharmacovigilance case reports are received from worldwide sources, including countries where non-prescription status is already approved (Bulgaria, Finland, Poland, and Sweden). However, the non-prescription status is not mentioned in the reported cases.

A number of 370 cases were received in Teva safety database (DLP 28 February 2019), of which the majority (n=287) were not serious cases.

Cardiovascular effects

- QT prolongation

The latest period safety update single assessment (PSUSA) reviewed the risk of QT prolongation. There were a number of publications presented that led to the conclusion that QT prolongation may be a risk with the use of desloratadine[4,5,6]. The PRAC concluded that a possible association desloratadine QT prolongation cannot be excluded based on this literature review. The product information was updated to include the ADR 'QT prolongation' with a frequency unknown in section 4.8 of the SmPC. In addition, due to the possible life-threatening cardiac effects that may be caused by QT prolongation, and according to PSUSA recommendation, the risk of QT prolongation will continue to be monitored as important potential risk.

- Supraventricular tachyarrhythmia, atrial fibrillation, atrial flutter

The PSUSA for desloratadine containing medicinal products also recommended to continue monitoring supraventricular tachyarrhythmia, atrial fibrillation, atrial flutter, being considered important potential risks.

Teva database contains 17 cases reported on adult patients, who experienced tachycardia, palpitations or heart rate increased during desloratadine administration. Most of the cases contained limited information for establishing the causality, however in 6 cases, 3 serious and 3 not serious, the events resolved after drug discontinuation and the causality cannot be excluded.

The majority of cases were not serious (n=13) and the event resolved in most of them (n=7), did not resolve at the moment of reporting in 4 cases and the outcome was unknown in 2 cases.

One case reported atrial fibrillation in 65- year- old patient and although medical history is not reported, the event resolved after drug discontinuation and the causal relationship cannot be excluded.

Tachycardia and palpitations are mentioned in the SmPC with a very rare frequency and based on the data available up-to-date, it is considered that the risk is appropriately covered in the product information and there is not new data that warrants further measures.

[4] Watson S. Desloratadine and QT prolongation. Uppsala Monitorig Centre. WHO Pharmaceuticals Newsletter No. 2, 2015.
[5] Godman B, Poluzzi E, Raschi E et al. Pro-arrhythmic risk of oral antihistamines (H1): Combining adverse event reports data with drug utilization data across Europe. *Basic Clin Pharmacol Toxicol*. 2014;115(1):83.
[6] Poluzzi E, Raschi E, Godman B et al. Pro-Arrhythmic Potential of Oral Antihistamines (H1): Combining Adverse Event Reports with Drug Utilization Data across Europe. PLoS One. 2015; 10(3): e0119551

Furthermore, the product information of the reference product was recently updated based in the results of a non-interventional non-imposed PASS study designed to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter (EUPAS15038).

The study found an association between current use of desloratadine and risk of first atrial fibrillation or flutter that persisted after adjustment for preselected confounders (aIRR 1.06, 95% CI 1.01; 1.12). In age-stratified analyses, the association was strongest for patients aged ≥ 65 years (aIRR 1.08, 95% CI 1.02; 1.15). In view of the results of this PASS, further information is required regarding the risk of A-fib/flu in special patient groups and seizure. This will be addressed in the next PSUR by the MAH in 2021.

The study found no association between current use of desloratadine and risk of first SVT. However, this risk will continue to be monitored as important potential risk.

- First seizure/ first recurrence of seizure

First seizure/first recurrence of seizure has also been studied in the PASS EUPAS15038. An absolute increase in incidence rate of first seizure of 42 per 100,000 patients-year in the 0-4 years age group has been seen in the study, which means 1 additional incident seizure for every 2,392 children aged 0-4 years using desloratadine for one year. Among children and adolescents 5-19 years of age, the absolute increase in incident rate was 17.3 per 100,000 patient-year, meaning one additional incident for every 5,870 children or adolescent aged 5-19 years receiving desloratadine for one year. No association was found of first seizure and desloratadine use in patients aged above 20 years.

The product information already includes a special warning and precaution for use on seizures, in addition, it is listed as an adverse reaction with a frequency very rare. Nonetheless, based on the results of this study, the section 4.8 of the SmPC of the reference medicinal product Aerius was updated to reflect the increased incidence of new-onset seizure in patients 0 to 19 years of age receiving desloratadine compared with periods not receiving desloratadine.

As the indication is proposed to be restricted to adults only, it is considered that this does not present an issue for the change of prescription status.

- Movement disorders (tics, dystonia, extrapyramidal symptoms)

An article[7] related to movement disorders has been published during the reference period, showing that desloratadine increased choice reaction time and tremor and concluded that desloratadine has the potential to affect movement control. In addition, this ADR was added in the safety labelling for desloratadine containing-products by the FDA.

Following the latest PSUSA, the MAHs of the centrally authorized desloratadine-containing products were requested to provide a further analysis of all available data regarding movement disorders (including dystonia, tics and extrapyramidal symptoms). The MAH submitted the analysis. Overall, it was concluded that the evidence from different sources is not suggestive of an association between desloratadine use and the occurrence of movement disorders. Based on the available data movement disorders were not added to the SmPC and the MAHs were requested to keep the "movement disorders" as ongoing safety signal and discuss it in future PSURs.

A search in Teva database using the search criteria HLGT Movement disorders (including parkinsonism) revealed 2 children cases that reported dystonia that are not relevant for this application. Three adult cases reporting psychomotor hyperactivity (n=2) and one case reported tremor, all cases being not serious and the events resolved after drug discontinuation.

[7] Preshanta Naicker, Shailendra Anoopkumar-Dukie, Gary D Grant, Justin J Kavanagh. The effects of antihistamines with varying anticholinergic properties on voluntary and involuntary movement. Clin Neurophysiol. 2013 Sep;124(9):1840-5. doi: 10.1016/j.clinph.2013.04.003. Epub 2013 May 3.

Based on the available information, the risk is not considered an important risk for the adult population.

Standard pharmacovigilance measures like close monitoring of movement disorders should be continued.

Drug interactions

Desloratadine does not inhibit CYP3A4 *in vivo*, and *in vitro* studies have shown that the medicinal product does not inhibit CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

No clinically relevant interactions were observed in clinical trials with desloratadine tablets in which erythromycin or ketoconazole were co-administered. In a clinical pharmacology trial desloratadine tablets taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol. However, cases of alcohol intolerance and intoxication have been reported during post-marketing use. Therefore, caution is recommended if alcohol is taken concomitantly.

During the latest PSUR period (Procedure no.: EMEA/H/C/PSUSA/00000962/201607) one publication was identified in the worldwide scientific literature on myotoxicity due to possible interaction between desloratadine and simvastatin.[8] Considering the extensive use of both drugs, the PRAC considered that this issue should be a new safety signal and should be carefully monitored.

No case reporting drug interaction with statins was received in Teva database. Four cases that reported drug interactions were received. In one non-serious case the interaction with pantoprazole leading to worsening of acid reflux was suspected and after taking the drugs at 10 hours interval, the symptoms improved. Another serious case reported the interaction with Alutard (used for immunotherapy for mite dust allergy) causing hepatic function abnormal. The fourth case reported drug interaction with levocabastine (selective second-generation H1 receptor antagonist used in allergic conjunctivitis).

All these cases reported in post-marketing confirm that based on the current data and considering the extensive use of the product, the risk of drug interaction is very low and does not represent a safety concern for this product.

Abnormal hepatic function (including hepatitis and elevated hepatic enzymes and bilirubin)

Abnormal hepatic function was reported in 8 adult patients. Three cases reported hepatic enzymes increased and one case of hepatotoxicity, but all cases were confounded by patient's medical history (alcohol consumer in the past- two cases), co-suspect drug(s) (n=2). Another case reported hepatic infection with very limited information provided and a serious case reported hepatic cytolysis, but multiple drugs were co-suspects. The seventh case reported hepatic function abnormal due to suspected drug interaction with Alutard. All cases are confounded by other factors; therefore a direct causality between desloratadine and the hepatic effects cannot be determined. The currently available data does not bring additional data that would classify this risk as a safety concern for the adult population.

Photosensitivity

One not serious case reported photosensitivity reaction in an elderly female patient, but the case contained very limited information for a proper assessment. Due to the low number of cases when compared to the extensive patient exposure, this risk is considered not important for desloratadine.

Use in patients with severe renal insufficiency

The pharmacokinetics of desloratadine in patients with chronic renal insufficiency (CRI) was compared with that of healthy subjects in one single-dose study and one multiple dose study. In the single-dose study, the exposure to desloratadine was approximately 2 and 2.5-fold greater in subjects with mild to

[8] Han X, Quinney SK, Wang Z, Zhang P, Duke J, Desta Z, Elmendorf JS, Flockhart DA, Li L. Identification and Mechanistic Investigation of Drug-Drug Interactions Associated with Myopathy: A Translational Approach. Clin.Pharmacol.Ther. 2015; 98(3): 321-327. 10.1002/cpt.150

moderate and severe CRI, respectively, than in healthy subjects. In the 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 CRI and ~2.5-fold greater in subjects with severe CRI. In both studies, changes in exposure (AUC and Cmax) of desloratadine and 3-hydroxydesloratadine were not clinically relevant. (SmPC)

According to the SmPC, in the case of severe renal insufficiency, desloratadine film coated tablets should be used with caution.

No case in Teva database reported use of desloratadine in patients with renal impairment. The use of desloratadine in patients with severe renal impairment is not considered a safety concern.

Use in pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of desloratadine during pregnancy.

Three cases reported use of desloratadine in Teva database. One of them reported drug reaction with eosinophilia and systemic symptoms in a pregnant woman who was receiving multiple drugs and the desloratadine implication cannot be determined. The other two cases reported exposure during pregnancy, no other adverse drug reactions and a normal newborn in one case. Based on this data it is concluded that use in pregnancy is not a safety concern for desloratadine.

Use in lactation

Desloratadine has been identified in breastfed newborns/infants of treated women. The effect of desloratadine on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from desloratadine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

No case reporting use in lactation was received in safety Teva database.

Considering the limited data available, the risk of use in lactation is considered missing information and it will be further monitored through routine pharmacovigilance activities.

Misuse, accidental or intended overdose or higher doses

The adverse event profile associated with overdosage, as seen during post-marketing use, is similar to that seen with therapeutic doses, but the magnitude of the effects can be higher. Based on a multiple dose clinical trial, in which up to 45 mg of desloratadine was administered (nine times the clinical dose), no clinically relevant effects were observed.

Eight cases reporting overdose were received in Teva database. Three cases reported multiple drug overdoses, of which one in a suicide attempt. In three cases prescribed overdose was reported and one accidental overdose by medication error, all cases being not serious and reporting mild adverse drug reactions (abdominal pain, fatigue, weight increased, face edema, sleep restless, and drowsiness). The last overdose case did not report any adverse event or any other information. Two cases of abuse with multiple drugs were received, one of them in a suicide attempt and the other with no adverse event reported One case reported misuse in a patient who administered two tablets instead of one due to lack of drug effect and no adverse event was reported.

A recent publication [9] reviews the available data regarding the overdose effects of non-sedating antihistamine drugs. The conclusion was that the clinical effects are generally not as marked as for

[9] Simon HL Thomas; Antihistamine poisoning; published on 03/2016; Medicine Elsevier; 44 (3) p.141-142)

sedating antihistamines, with a low propensity for sedation, anticholinergic and cardiovascular effects. Severe clinical effects are uncommon, even with very large doses. Clinical features following overdose are non-specific and include tachycardia, drowsiness or agitation, gastrointestinal disturbances, dizziness and headache. The older non-selective agents terfenadine and astemizole produced QT interval prolongation and torsade de pointes when taken in overdose and sometimes after therapeutic dosing, resulting in these drugs being withdrawn from the market. There have been occasional reports of QT prolongation or arrhythmia with therapeutic doses of newer agents (e.g. loratadine), but if there is a risk, it appears very small. Metabolic acidosis, seizures and cardiac arrest have been reported rarely after massive overdose.

The cases received by Teva which are in accordance with SmPC information and the literature data prove that the health consequences for the patients in case of misuse, overdose, increased dose, abuse are mild and limited.

Discussion

Overall, based on all the data analysed above (including case reports received from countries where non-prescription status is already approved), the MAH concluded that for the adult population for which the switch of the prescription status to non-prescription is intended, the adverse drug reactions that may occur are in general mild to moderate and limited and even if severe adverse drug reactions (QT prolongation, arrhythmias, seizures, hepatitis) may occur, the frequency of occurrence is very rare relative to an extensive patient exposure.

7. Evaluation of criteria for classifying a medicinal product as subject to medical prescription or not

According to the "EU Guideline on changing the classification for the supply of a medicinal product for human use, Rev. January 2006", a number of criteria should be taken into consideration for classifying a medicinal product as not subject to medical prescription.

These four criteria are:

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision
2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health
3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation
4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

Criterion 1: Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

A summary of the MAH's justification for the first criterion is provided below.

1.1 Direct danger/ safety profile

(a) A direct danger, when the product is used correctly, (according to the patient information), encompasses toxicity, interactions and adverse reactions. A medicinal product not subject to a medical prescription should have:

-low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties;

-low risk of serious type A2 adverse reactions in the general population.

-very low risk of serious type B3 reactions;

-no interactions with commonly used medicines which can produce serious adverse reactions, [see also 1.5 c)].

(b) The criterion of danger can take account of the possibility of preventive action. For example, serious type A reactions can be acceptable if there is a clear identifiable risk group that can be excluded even in the absence of medical supervision.

(c) The safety of a medicinal product is relative to that of the alternative treatment.

Toxicity profile

Desloratadine is the primary active metabolite of loratadine. 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. 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.

Clinical safety profile

Overall, the safety profile of desloratadine includes ADRs for which seriousness is mild to moderate (see section 6.). There are few ADRs, which are serious and, in some cases, may become life threatening. The hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticaria) may occur but the frequency is very rare (< 1/10,000), QT prolongation, for which the frequency of occurrence is not known. The QT prolongation risk was assessed in section 6. . Based on the available data and considering that pre-clinical studies did not demonstrate a role in cardiac repolarization impairment [10] the MAH concluded that a strong association is not proven. Nevertheless, a possible association desloratadine- QT prolongation cannot be excluded based on the literature review especially when associated with other drugs known to induce QT prolongation. Seizures and hepatitis are other two serious risks, seizures occurring especially in children, and both may very rarely occur.

Interactions

The pharmacokinetics data currently available show that desloratadine does not inhibit CYP3A4 *in vivo*, and *in vitro* studies have shown that the medicinal product does not inhibit CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein. In addition, clinical trial data and clinical pharmacology studies performed up until now, as presented in section 6. , Drug interactions, did not reveal alcohol interaction. The post marketing data showed a possible alcohol intolerance and the interaction with simvastatin leading to myotoxicity (known adverse drug reaction for simvastatin) is under monitoring. Nevertheless, the analysis of currently available data leads to the conclusion that there is no enough

[10] Torsade De Pointes and QT Prolongation Could Result From Desloratadine AntiAllergy Treatment. Ali AK. *Value Health*. 2015 Nov;18(7):A493-4.)

supportive data for desloratadine interacting with commonly used medicines in the general population and causing serious adverse reactions.

Considering all of the above, the MAH concluded that, when the product is used correctly, (according to the patient information), the risk of direct danger, which encompasses toxicity, interactions and adverse reactions, is expected to be very low for desloratadine.

1.2 Indirect danger/safety profile

(a) An example of indirect danger, even when the product is used correctly, that is to say used according to the patient information, would be where symptomatic treatment might mask/hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy. Package leaflet and or label warnings may be necessary to prevent treatment from "masking" the development of a serious disorder. Therefore, such warnings should indicate a time limit beyond which, if symptoms persist, medical advice should be sought. Medicinal products not subject to a medical prescription should be approved primarily for short term treatment, e.g. when the possibility of "masking" could occur.

The approved indications for desloratadine are allergic rhinitis and urticaria. Allergic rhinitis is an inflammation of the nasal membranes that is characterized by sneezing, nasal congestion, nasal itching, and rhinorrhoea, in any combination. Urticaria is a vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated papules or plaques (wheals) that are erythematous and that are often attended by severe pruritus.

When the patient experiences a first episode of allergic rhinitis or urticaria, due to the symptomatology, which can be distressing for both medical conditions, it is most likely that they will address to a physician and appropriate treatment is applied. When the episode is not a new one, the patients already know their disease, and they are likely to be able to manage their condition. Furthermore, according to the patient information leaflet, the patients are clearly instructed to ask the doctor or pharmacist, if they need advice.

In conclusion, is the MAH evaluated that the risk for masking an underlying condition, which needs medical supervision and attention, is low. Furthermore, even if the patient may wrongly assess his condition if never diagnosed with these diseases before and this may delay the diagnosis, the risk for severe health consequences is considered low by the MAH.

(b) An indirect danger is also present if wider use of a medicinal product would increase the risk of resistance to the product, in particular in the general population, to such an extent that the usefulness of any medicinal product is likely to be compromised; or if the symptom is commonly the outward manifestation of a diverse range of underlying pathologies and where the patient cannot easily discern the underlying disease.

Based on the currently available pharmacokinetic data, clinical trials and post marketing data, is the MAH assessed that there is no risk of resistance to the product in general population. The possibility that the patient cannot easily discern the underlying disease is discussed in details, below at point 1.3.

1.3 Self-assessment

(a) It is important that the condition or symptoms, for which a medicinal product not subject to a medical prescription is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision. This means that the patient should be capable of excluding conditions which could appear to be similar to the indications but unsuitable for treatment with the medicine in question.

Account may be taken of the availability of appropriate information sources that would assist the patient in achieving this, including written information or the advice of pharmacist and other health care professionals.

The symptomatology in allergic rhinitis may be similar to an acute sinusitis or chronic sinusitis, especially a sinusitis caused by a viral infection, which represents the vast majority of rhinosinusitis episodes. In about 0.5-2% of cases, an acute viral sinusitis can progress to acute bacterial sinusitis [11], for which the symptomatology is more severe and different from an allergic rhinitis, with pain, fever, malaise and which necessitates different medical intervention. Due to general deterioration of the symptomatology, that is specific for infections, the patient will most likely refer to a physician.

Urticaria may be confused with a variety of other dermatologic diseases that are similar in appearance and are pruritic, including atopic dermatitis (eczema), maculopapular drug eruptions, contact dermatitis, insect bites, erythema multiforme, pityriasis rosea, and others.[12]

Individual lesions resolve without scarring in several hours. Most cases of urticaria are self-limited and of short duration; the eruption rarely lasts more than several days, but it may be recurrent over weeks. Chronic urticaria is defined as urticaria with recurrent episodes lasting longer than 6 weeks. Acute urticaria may be, in a short time, associated with life-threatening angioedema and/or anaphylactic shock, although it usually presents as rapid-onset shock without urticaria or angioedema.

However, these conditions wrongly self-diagnosed by the patient as allergic rhinitis or urticarial are in general mild and self-limited medical conditions; therefore the MAH considers that the use of desloratadine in these cases does not pose the patient to severe risks and even may have beneficial effects in some of them.

(b) The natural course of the disease, the condition, the duration of symptoms and their reoccurrence and consequences due to this should be correctly self-assessable.

Allergic rhinitis is a condition that manifests as long as the patient is exposed to a certain allergen, the symptoms being disturbing for the patient (sneezing, itching: nose, eyes, ears, palate, rhinorrhoea, postnasal drip, congestion, anosmia, headache, earache, tearing, red eyes, eye swelling, fatigue, drowsiness, malaise). Allergic rhinitis itself is not life-threatening (unless accompanied by severe asthma or anaphylaxis), however morbidity from the condition can be sometimes significant as allergic rhinitis can cause sleep disturbances, otitis, and sinusitis.[13]

The development of urticaria is often an isolated event without systemic reaction. Acute and chronic urticaria can result in severely impaired quality of life from pruritus and associated sleeplessness, as well as anxiety and depression[14]. Most cases of urticaria are self-limited and of short duration; the eruption rarely lasts more than several days, but may be recurrent over weeks. Chronic urticaria is defined as urticaria with recurrent episodes lasting longer than 6 weeks. Individual lesions resolve without scarring in several hours.[12] Rarely, it can be a prelude to the development of an anaphylactic reaction. .

For acute urticaria in patients who have never been diagnosed with urticaria, there are some risks. First, there is a risk that other dermatological conditions, as mentioned above are misdiagnosed and treated with desloratadine. However, most of these skin conditions are self-limited or for some of them antihistaminic treatment may be useful. Secondly, there is a risk that acute urticaria may rarely evolve to

[11] Itzhak Brook, MD, MSc; Chief Editor: Michael Stuart Bronze, MD; Acute sinusitis (Medscape); updated Mar 01, 2018; retrieved on May10, 2019 from https://emedicine.medscape.com/article/232670-overview#a
[12] Henry K Wong, MD, PhD; Chief Editor: Michael A Kaliner, MD; Acute urticaria (Medscape); retrieved on Mar 21, 2018 from https://emedicine.medscape.com/article/137362-overview#a6
[13] Javed Sheikh, MD; Chief Editor: Michael A Kaliner, MD; Allergic Rhinitis (Medscape); updated Dec 2018; retrived on May 10, 2019 from https://emedicine.medscape.com/article/134825-overview
[14] Henry K Wong, MD, PhD; Chief Editor: Dirk M Elston, MD; Urticaria (Medscape); updated Jun 13, 2018; retrieved on May 13, 2019 from https://emedicine.medscape.com/article/762917-overview#a3

a life-threatening angioedema and/or anaphylactic shock and patients that were previously diagnosed by a physician may not understand the initial symptoms or the health consequences.

For chronic urticaria, it is likely that the patients had been previously diagnosed and explained the possible evolution of the symptoms and possible life-threatening outcome; therefore they are more aware of what they need to do or when to contact the physician in case the symptoms get worse.

Based on IQVIA MIDAS sales data for period Sep/2008 to Sep/2018 in the EU the percentage of desloratadine sold as OTC out of the total sales was 2%. In addition, for the period Sep/2014 to Sep/2018 based on IQVIA MIDAS sales data, for Teva the percentage was 0.7% and for other MAHs in the EU, the percentage was 1%.

The MAH considered that there is a low risk for patients that have never been previously diagnosed with urticaria to misdiagnose and not properly manage their disease. In addition, considering the fact that there is not an extensive use as non-prescription in EU for Teva or other MAHs for desloratadine and that loratadine is approved as chronic idiopathic urticaria in Teva, the MAH agreed that for desloratadine, chronic idiopathic urticaria is a more appropriate indication for a non-prescription medicine.

Based on the above and the fact that the indications for desloratadine are mild in most of the cases, self-limited and well known if it is not the first episode, the MAH evaluated that the patients are capable to predict the natural course of the disease, reoccurrence of the symptoms and ask for appropriate medical advice, if needed.

(c) Contraindications, interactions, warnings and precautions should be those which can be understood by the consumer.

There is one contraindication listed in section 4.3 of the SmPC (Hypersensitivity to the active substance, to loratadine or to any of the excipients listed in section 6.1.) which is common for all drugs and which is likely to be clearly understood especially by patients with allergic conditions. There are three warning and precautions mentioned in the SmPC referring to patients with severe renal impairment, patient with seizures (especially children who are out of the scope) and patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption. All of them are chronic medical conditions and usually well understood by the patients.

1.4 Risk and consequences of incorrect use

(a) A high incidence of conditions listed as contraindications, precautions or warnings, or a high rate of usage of interacting drugs in the population, in case of patients likely to use the medicine, may increase the incidence and risk of misuse; (see below, 1.5 Patient information).

Urticaria is a condition that occurs most commonly in children and young adults.[12] The development of allergic rhinitis before 20 years of age occurs in 80% of cases [11]. Consequently, the likelihood that the target population uses multiple drugs that may interact with desloratadine is low. Furthermore, the listed medical conditions as contraindications, precautions or warnings (severe renal impairment, patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, seizures) are chronic conditions and patients are under regular medical supervision, which may prevent for the misuse.

(b) It is important that the danger to health is small, if the patient uses the product where it is not indicated, uses it for a longer period than recommended, exceeds the recommended dose or fails to heed warnings or contraindications. Consideration of the consequences of misuse is an important component of the overall safety profile of the medicinal product which should be reflected in the label (as provided for in Article 54 g) and n) of Directive 2001/83/EC and/or the package leaflet.

The patient information leaflet offers clear instructions on the symptomatology and on how long the medicinal product should be used until medical advice is to be sought. In addition, the outer packaging contains information on how many tablets should be administered per day (one tablet per day). All these measures are intended for mitigating the risk for misuse.

1.5 Patient information

(a) The way in which a medicinal product not subject to medical prescription is used is likely to differ from the way the same product was used when available only on prescription, even when the indications are the same or in the same therapeutic area. There is also the risk that the patient will consider the medicinal product not subject to a medical prescription as being less dangerous than when the same product is subject to a medical prescription. This should be taken into consideration.

The patient information leaflet and outer packaging reflect the legal status 'not subject to medical prescription' by using the appropriate QRD template for medicines available without a prescription. As a consequence thereof, it is clearly stated in the patient information leaflet, that the patient should ask the doctor for advice if he does not feel better or does feel worse after taking the medicinal product. In consideration of the fact that taking one tablet will result in relieving the symptoms for one day the patient is therefore obliged to talk to the doctor even after one day.

The change in the indication is reflected by stating the patient target group in a prominent way on the front panel of the outer packaging, i.e. in section 15 of the QRD template, and right at the beginning of the patient information leaflet.

(b) The written information (package leaflet and label) must contribute effectively to safe and effective use of the medicine. The correct use of the medicine should be explained in the information. It is necessary to consider if the information is clear enough for the patients to use the medicine appropriately. This information should be sufficient so that it substitutes for the absence of medical supervision.

The results of the readability testing show that the percentage of participants successfully finding the section and answering the questions correctly was within the acceptable percentage outlined in the protocol. All participants thought the readability of the Desloratadine ratiopharm Patient Information Leaflet was good. There was no information included in the leaflet that they could not understand or follow. Although some suggestions were made as to how people felt that the leaflet could be improved most of these related to positioning of information which is defined by the QRD format. Overall, the feedback was positive and this was supported by the results of the user testing process. No changes are needed to the layout or content of the Patient Information Leaflet following testing.

In general, participants could easily find their way around the leaflet and all participants were able to give the correct answers, although one participant was unable to answer one question. No changes were made to the PIL during the user testing process therefore no further testing is required.

(c) The written information supplied with the medicine, in addition to the supervision of the pharmacist when applicable, should be adequate to guard against a risk of using the product where it is contraindicated or unsafe. Contraindications, interactions, warnings and precautions need to be clearly described in layman's terms and prominently presented in the leaflet. See also the guideline on the readability of the label and package leaflet.

As demonstrated by the outcome report of the Readability Testing, the relevant information about contraindications, interactions, warnings and precautions is legible, clear and easy to use for patients.

(d) In order to minimise risk and maximise benefit, the leaflet and the label should describe the situations where the product should not be used, in at least as much detail and prominence as to when it may be used (see above, 1.4 Risk and consequences of incorrect use) and in accordance with the summary of

product characteristics. The patient is likely to need guidance on action to take if the medicine does not have the desired effect or cause an adverse effect. The product information (package leaflet and label) should in such cases recommend appropriate action e.g. consulting a doctor or a pharmacist within the time stated in the label/package leaflet.

Situations, in which the product should not be used are described in detail in the patient information leaflet and are in accordance with the summary of product characteristics. The outcome report of the Readability Testing clearly demonstrates that patients are able to find and understand in which situations they need to seek advice from a doctor before using this medicine and in case the medicinal product does not have the desired effect.

CHMP discussion on first criterion

First criterion: Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

(1.1) The CHMP has considered the safety profile of Desloratadine ratiopharm in order to ensure that it is not likely to present **a direct danger even when used correctly, if utilised without medical supervision.**

Non-clinical studies are reassuring for both loratadine and desloratadine and do not show any signs for special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Adverse events for desloratadine are usually mild or moderate and thus has a low general toxicity. As mentioned in the Article 5(3) referral, when administered at standard clinical doses according to the terms of the marketing authorisation, the safety profile and clinical effects of desloratadine are expected to be similar to those of loratadine[3].

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foeto/ neonatal toxicity of desloratadine. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of desloratadine during pregnancy. The product information is considered up-to-date and no changes are proposed regrading use in pregnancy. With regard to breast-feeding, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from desloratadine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. The section 4.6 of the SmPC is updated to state that breast-feeding women shall seek medical advice before using desloratadine. Use in lactation is also listed as a missing information in the summary of safety concerns in the RMP. The section 2 of the package leaflet is updated accordingly.

The uncertainties discussed during the Article 5(3) referral about the direct danger regarding supraventricular arrhythmia, atrial fibrillation and atrial flutter (A-fib/flu), seizures as well as regarding movement disorders have since then been assessed in the Nordic register-based study (EUPAS15038) (procedure numbers: MEA 065; EMEA/H/C/WS1655).

The study found no association between current use of desloratadine and risk of first SVT. No regulatory actions were considered necessary, also taking into account limited evidence from spontaneous reporting. Further monitoring is to be performed by means of routine pharmacovigilance and SVT should be listed as an important potential risk in the summary of the safety concerns in the RMP.

At the time of the study review, the MAH concluded that evidence is insufficient to conclude that the association between current desloratadine use and A-fib/flu is causal. However, in view of the results of

this study, PRAC considered that further information is required regarding the risk of A-fib/flu in special patient groups and should be further addressed next PSUR by the MAH in 2021.

The study also indicated an increased incidence of new-onset seizure in patients 0 to 19 years of age when receiving desloratadine compared with periods not receiving desloratadine. The section 4.8 of the SmPC of the reference product Aerius was therefore updated to reflect the increased incidence of new-onset seizure in patients 0 to 19 years of age receiving desloratadine compared with periods not receiving desloratadine. No association was found of first seizure and desloratadine use in patients aged above 20 years. Although Desloratadine ratiopharm is now indicated only for adults, the section 4.8 of the SmPC of should be updated in this variation in accordance with the reference product to reflect the current safety knowledge.

The evidence from different sources is also not suggestive of an association between desloratadine use and the occurrence of movement disorders.

Tachycardia and palpitations are mentioned in the SmPC with a very rare frequency and based on the data available up-to-date, it is considered that the risk is appropriately covered in the product information and there are no new data that warrant further measures.

QT prolongation has been listed as an ADR in section 4.8 of the SmPC with a frequency not known in the latest PSUSA. No statistically or clinically relevant effects have been observed in clinical trials. Therefore, no further change is proposed at the moment in the product information.

Abnormal hepatic function was reported in 8 adult patients. All cases are confounded by other factors; therefore, a direct causality between desloratadine and the hepatic effects cannot be determined. However, elevations of liver enzymes, increased bilirubin, hepatitis are listed as very rare events with jaundice unknown. Therefore, in the case of severe hepatic impairment, desloratadine should be used with caution, as hepatitis and jaundice are possible adverse reactions. A warning in section 4.4 of the SmPC is included in this variation. The section 4.8 of the SmPC and section 4 (possible side effects) of the package leaflet already include the adverse reactions elevations of liver enzymes, increase bilirubin, hepatitis (liver inflammation and abnormal liver function tests) with a frequency very rare and jaundice (yellowing of the skin and/or eyes) with a frequency not known.

There are no known interactions with commonly used medicines.

Based on the safety profile, CHMP considered that Desloratadine ratiopharm is not likely to present a direct danger when used correctly, if utilised without medical supervision, in the adult population.

(1.2) With regard to the **absence of indirect danger**, CHMP agrees that the risk of masking and or hiding underlying conditions is highly unlikely when it is used in the authorised conditions. Allergic rhinitis is a self-limiting disease, and for a first episode of allergic rhinitis, it is most likely that a patient will have sought a physician for appropriate treatment. For a next episode of allergic rhinitis, symptoms are known and patients already know their disease and they can self-manage their disease. For chronic idiopathic urticaria, it is specifically mentioned it needs to be diagnosed initially by a physician, which limits the indirect danger for non-prescription use. The product information advises patients to seek medical advice if symptoms persist for more than 7 days or deteriorate in order to minimise the risk of masking an underlying disease. There is no risk of increased resistance to desloratadine, based on currently available pharmacokinetic data, clinical trials and post-marketing data.

(1.3) CHMP considered the **self-assessment of the condition** by patient as follows:

Allergic rhinitis is a condition that manifests as long as the patient is exposed to a certain allergen. The symptomatology in allergic rhinitis may be similar to an acute sinusitis or chronic sinusitis, especially a sinusitis caused by a viral infection, which represents the vast majority of rhinosinusitis episodes, a minority may progress to bacterial infection. Allergic rhinitis itself is not life-threatening (unless

accompanied by severe asthma or anaphylaxis). The package leaflet provides adequate description of the allergic rhinitis symptoms and advise the patient to consult their doctor if the symptoms persist for more than 7 days or deteriorate.

With regard to the indication urticaria, CHMP acknowledges that the condition may be confused with a variety of other dermatologic disease, as it can be similar in appearance and pruritic, such as atopic dermatitis (eczema), maculopapular drug eruptions and others. This is in particular applicable to acute urticaria which may wrongly be assessed by the patient if never diagnosed with the condition and may also delay the diagnosis. For chronic urticaria, the patient should have been diagnosed by a physician and should be able to recognise the symptoms. Therefore, taking into account the risk of misdiagnosis or progression to a life-threatening angioedema and/or anaphylactic shock (as well as no extensive non-prescription medicine experience with desloratadine nor loratadine in the acute urticaria indication), CHMP considers that the urticaria indication should be restricted to 'chronic idiopathic urticaria as initially diagnosed by a physician' if the product is to be used in a non-prescription setting. In addition, a warning in section 4.4 of the SmPC is added to state that chronic idiopathic urticarial should initially by diagnosed by a physician. In case of symptom that indicate angioedema, the patient needs to seek medical help immediately. The package leaflet is updated accordingly with the corresponding warnings.

Both indications (allergic rhinitis and chronic idiopathic urticaria) have already been accepted as non-prescription indication for many other medicinal products. It is considered that the vast majority of the targeted patients can properly assess their symptoms without medical supervision. This is even more likely considering the indication has been limited to adults only. Appropriate information about the description of the symptoms are included in the package leaflet. Patients are also advised to consult their doctor or pharmacist, if they need advice.

(1.4) **Risk and consequences of incorrect use** are considered low and can be effectively mitigated by the information in the package leaflet, SmPC and labelling. The listed medical conditions as contraindications, precautions and warnings are chronic disease and are chronically supervised. These chronic patients will also know their status which limits incorrect use. Clear instructions on symptomatology and posology, as well as instructions on when to seek additional advise from a physician are present in the patient leaflet.

(1.5) With regard to the **patient information**, the written information (package leaflet and label) has been updated and the CHMP considered that the changes were adequate to contribute effectively to safe and effective use of the medicine. The information on the correct use of the medicine is explained in the proposed package leaflet. In order to ensure that this information on how to use the medicine appropriately is clear enough for the patients, a readability testing has been performed among representatives of the target population. The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Contra-indications, interactions, warning and precautions are few and can be readily understood in lay language.

CHMP conclusion on the first criterion

In view of the above discussion, the CHMP considered that Criterion 1 of the Article 71 of Directive 2001/83/EC and European Commission Guideline "Medicinal products shall be subject to medical

prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision" does not apply.

Criterion 2: Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

The following justification has been provided by the MAH for the second criterion.

Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

In considering whether this criterion applies, the following factor should be addressed.

2.1 Known incorrect use

Known incorrect use for products not subject to a medical prescription (e.g. used for increasing the effects of alcohol), could lead to restrictions on the product or reclassification for supply subject to a medical prescription (see also 6. Other Considerations on page 7). Under such circumstances, classifying the medicinal product as not subject to a medical prescription should not be considered.

In a clinical pharmacology trial desloratadine tablets taken concomitantly with alcohol did not potentiate the performance impairing effects of alcohol. However, cases of alcohol intolerance and intoxication have been reported during post-marketing use. Therefore, caution is recommended if alcohol is taken concomitantly. Even if the possible drug interaction with the alcohol is listed in the SmPC based on the reported post-marketing use, based on the data analysed in section 6. 'Drug interaction', it is assessed that this risk is low. In addition, considering the available data of misuse, abuse and overdose (Teva case reports and literature) it is concluded that the health consequences for the patients in case of misuse, overdose, increased dose, abuse are mild and limited (Section 6. 'Misuse, accidental or intended overdose or higher doses').

CHMP discussion on second criterion

Known incorrect use is low and does not pose a direct or indirect danger to human health. Appropriate information is already included in the sections 4.5 and 5.1 of the SmPC regarding interaction with alcohol. The section 2 of the package leaflet also states to use caution when taking desloratadine ratiopharm with alcohol. The section 4.9 of the SmPC concerning 'overdose' is considered up to date. The section 3 of the package leaflet also advises patients to consult their doctor/ pharmacist immediately in case they take more desloratadine than as recommended.

CHMP conclusion on second criterion

In view of the above discussion, the CHMP considered that Criterion 2 of the Article 71 of Directive 2001/83/EC and European Commission Guideline "Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health" does not apply.

Criterion 3: Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation.

A summary of the justification provided by the MAH for the third criterion is provided hereafter.

3. Third Criterion

Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation. In considering whether this criterion applies, the following factors should be addressed.

3.1 Recent authorisation/limited experience

(a) Further investigation may be necessary when a medicinal product has only recently been granted a marketing authorisation or because of limited experience/use of the product e.g. low sales. Experience in other EU Member States and in other markets, which have sufficient post marketing surveillance, should be taken into consideration.

Desloratadine, Teva product has been on the market since 2012, while the reference product Aerius has marketing authorisation since 2001; hence, there is a long experience on the market. In addition, the patient exposure is significant, both as "prescription only" or non-prescription. Patient exposure, based on Teva sales data, worldwide cumulative exposure to Teva desloratadine 5 mg tablets until 31 January 2019 was 1.247.742.307 patient-days or 41.591.410 patient-months. EU exposure for the same cumulative period was 916.389.074 patient-days, and 30.546.302 patient-months.

Teva markets non-prescription desloratadine in Bulgaria, Finland, Poland, Sweden, while other MAHs have also non-prescription sales in Hungary and Denmark.

The MAH concluded that the experience with desloratadine both for Teva and other MAHs, either as "prescription only" or non-prescription is extensive, allowing for a good characterization of the safety profile.

(b) Even if clinical trial data are extensive and reassuring, it is important to have post-marketing experience in the general population, that is evidence of safety when the product is being used without the exclusion of certain groups of patients, which may be imposed by the design of clinical trials e.g. the elderly, children, certain racial or phenotypic groups and those having certain medical conditions. Products which have different safety or efficacy profiles in different racial or phenotypic groups may need special warnings.

Based on the IMS data, the postmarketing exposure included all age groups from zero to ≥ 66 and for both sexes. In addition, the majority of patients treated for allergic rhinitis and urticaria are prescribed with desloratadine or use it between 15 to 120 day, with up to 540 days of treatment.

The warning and precaution section of the SmPC and package leaflet mention the categories for which desloratadine should be used with caution (severe renal insufficiency, seizures and patient with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption). The desloratadine exposure included all age groups, both sexes, long treatment duration and few categories that need special warnings.

3.2 New strength, dose, route of administration, indication, new age group or combination of substances

Not applicable for this application.

CHMP discussion on third criterion

With regard to the **recent authorisation/ limited experience** criterion, CHMP agrees that patient experience with desloratadine is widespread, both as prescription and non-prescription medicines allowing for a good characterisation of the safety profile. In addition, a non-interventional non-imposed PASS study designed to assess the potential risk of desloratadine exposure on seizures, supraventricular tachycardia, and atrial fibrillation or flutter was completed (procedure numbers WS1655; MEA 065), as well as a post-authorisation measure (LEG 0066) concerning movement disorders (see section 6.).

Appropriate information was included in the product information following review of the PASS study and analysis.

With this variation the MAH does not apply for a new strength, dose or route of administration. However as a consequence of this variation, the urticaria indication and age group are restricted as mentioned in previous sections.

CHMP conclusion on third criterion

In view of the above discussion, the CHMP considered that Criterion 3 of Article 71 of Directive 2001/83/EC and the European Commission Guideline "Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side effects of which require further investigation" does not apply to Desloratadine ratiopharm.

Criterion 4: Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection).

4. Fourth Criterion

Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection).

This criterion is not applicable to Desloratadine ratiopharm since the product is not to be administered parentally (for injection).

Other considerations

According to Article 71(4) of Directive 2001/83/EC a medicinal product, which meets any of the criteria for supply subject to medical prescription, may be classified for supply not subject to medical prescription if: the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use, can make supply without medical prescription appropriate.

6.1 Pack size and package form (container)

(a) The pack size should be decided in relation to the intended length of the treatment. Restricting the availability of a medicinal product to a small pack size is a possible safeguard against misuse, particularly overdose, or a delay in seeking medical attention.

The duration of treatment of allergic rhinitis is variable. In order to treat the symptoms, for example, caused by allergens such as birch or grass pollen it might be necessary to take the medicinal product for several months. To reflect this, pack sizes from 7 to 100 tablets are available. The same range of pack sizes is available for loratadine containing medicinal products, which have been widely available in the majority of Member States as an OTC-medicinal product for a number of years.

In the patient information leaflet it is clearly stated to seek advice in case the patient does not feel better, the symptoms are getting worse or in case of overdose.

(b) Medicinal products should have a container which as far as possible prevents children gaining access to the medicine, if they get hold of the container.

The labelling for Desloratadine ratiopharm 5mg contains a warning: Keep out of the sight and reach of children. Considering the safety and toxicological profile of desloratadine, it is assessed that what is currently proposed for the packaging material is appropriate and no other measures are needed.

6.2 Maximum dose, maximum daily dose

Restricting the maximum dose or maximum daily dose may protect against potential danger whether the medicine is used correctly or incorrectly. However it is necessary to confirm that the reduced dose retains the efficacy.

The outer packaging (on the front panel) as well as the patient information leaflet clearly and precisely state, that the recommended dose is one tablet per day.

CHMP discussion on other considerations

Considering that seasonal allergic rhinitis can last for 6 weeks to even 3 months, it is considered necessary to limit pack size to 30 tablets. Therefore, the pack sizes of 40, 50, 60, 90 and 100 tables are deleted (EU/1/11/746/007-011). Therefore, the pack sizes of 40, 50, 60, 90 and 100 tables are deleted (EU/1/11/746/007-011). Clear recommendation to keep desloratadine out of sight and reach of children is already present in the outer packaging.

The outer packaging as well as the patient information contains clear and precise recommendations. This has been confirmed in the Readability Testing.

8. Risk management plan

Safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	Supraventricular tachyarrhythmia
Missing information	Use in lactation

Pharmacovigilance plan

None

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Risk minimisation measures

None

The safety information in the proposed product information is aligned to the reference medicinal product.

8.1. Overall conclusion on the RMP

☒ The changes to the RMP version 1.2 are acceptable.

9. Changes to the Product Information

As a result of this group of variations, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC are being updated to reflect the change of legal status and the restriction of the indication to adults only.

The Package Leaflet (PL) and labelling are updated accordingly.

Changes are also made to the product information to bring it in line with the current QRD template version 10.1, SmPC guideline and other relevant guidelines.

Changes are made to the Opinion Annex II conditions to reflect that desloratadine ratiopharm is a medicinal product not subject to medical prescription and to include the RMP requirements.

In addition, the list of local representatives in the PL is being revised.

9.1. Quick Response (QR) code

Not applicable

9.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.