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EMA/221731/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Votubia

International non-proprietary name: everolimus

Procedure No. EMEA/H/C/002311/X/0045

Note

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

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List of abbreviations

BHT	Butylhydroxytoluene
EC	European Commission
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
OOS	Out of Specifications
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RH	Relative Humidity
SDS	Sodium dodecyl sulphate
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
USP	United States Pharmacopoeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 23 June 2017 an extension of the marketing authorisation.

The MAH applied for addition of a new strength (1 mg dispersible tablet).

The MAH applied for the following indication for Votubia 1 mg dispersible tablet, in line with the existing indication of the authorised 2 mg, 3 mg and 5 mg dispersible tablets:

Refractory seizures associated with tuberous sclerosis complex (TSC)
Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).
Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)
Votubia is indicated for the treatment of adult and paediatric patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.
The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Information on Paediatric requirements

The application included an EMA Decision P/0003/2014 on the agreement of a paediatric investigation plan (PIP). PIP P/0003/2014 is completed. The PDCO issued an opinion on compliance for the PIP P/0003/2014.

In addition, the second PIP P/0316/2017 is not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Greg Markey

- The application was received by the EMA on 23 June 2017.
- The procedure started on 13 July 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 October 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 28 September 2017.
- During the meeting on 9 November 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 17 January 2018.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 22 February 2018.
- During the meeting on 22 March 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Votubia on 22 March 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The product Votubia (everolimus) has been approved for the following indications:

- Renal angiomyolipoma associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

The evidence is based on analysis of change in sum of angiomyolipoma volume.

- Refractory seizures associated with tuberous sclerosis complex (TSC)

Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).

- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)

Votubia is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

2.1.2. Epidemiology

TSC is a rare and debilitating disease with a prevalence of approximately 1 in 6000 live births (Krueger and Franz, 2008).

2.1.3. Biologic features

Tuberous sclerosis complex (TSC) is an autosomal dominant condition involving the TSC1 (encoding hamartin, chromosome 9) and/or TSC2 genes (encoding tuberin, chromosome 16).

Mutations in either TSC1 or TSC2 are found in 80% to 85% of patients and a wide spectrum of mutations results in mTOR hyperactivity.

Deficiency of either gene leads to upregulation of mTORC1 resulting in abnormal cellular growth, proliferation, and protein synthesis.

2.1.4. Clinical presentation, diagnosis

The disease expression is highly variable, with manifestations ranging from mild skin findings to seizures, learning disabilities, mental retardation, autism and fatal renal, cardiac or pulmonary disease.

Skin lesions occur in nearly all patients and are key to the recognition and diagnosis of TSC. Hamartomas in the brain usually present themselves in the form of subependymal nodules. Up to 20% of patients with TSC demonstrate progressive growth of the subependymal nodules, such that it becomes Subependymal giant cell astrocytoma (SEGA), which represents a significant medical risk for the patients, including potential sudden death secondary to acute hydrocephalus (Adriaensen et al. 2009). The majority of patients with TSC also have numerous bilateral renal angiomyolipoma.

In addition to growth abnormalities, patients with TSC usually develop epilepsy and neuro-psychiatric problems such as developmental delay, mental retardation, and autism (Curatolo et al. 2002; Levine et al. 2006). Epilepsy has been reported in up to 90% of individuals with TSC (Wong 2010), with an onset usually in the first years of life (with 82% before 3 years of age).

A limited number of features are responsible for the decreased life expectancy and these include:

- Neurologic disorders (SEGAs and seizures)
- Renal disease (angiomyolipomas)
- Pulmonary disease (lymphangioleiomyomatosis and bronchopneumonia)
- Cardiovascular disease (rhabdomyoma and aneurysm)

2.1.5. Management

Votubia is the only authorised treatment for adult patients with renal angiomyolipoma and subependymal giant cell astrocytoma associated with TSC. It has also been authorised for the refractory seizures associated with TSC.

In addition, vigabatrin (VGB) and adrenocorticotrophic hormone (ACTH) are considered to be mainstay therapies for the treatment of seizures in patients with TSC (Neuropsychiatric Disease and Treatment 2014:10 2021–2030).

About the product

Votubia contains the active substance everolimus, a rapamycin derivative, which acts as selective inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase within the mTOR-raptor signal transduction complex 1 (mTORC1) which is involved in the regulation of protein synthesis, cell growth, proliferation and survival. Due to its immunosuppressing activity, everolimus was initially developed to prevent allograft rejection following solid organ transplantation. It is approved under the tradenames Certican® and Zortress® in more than 80 countries worldwide for use in these indications. In the EU, everolimus is also approved under the tradename Afinitor® for the treatment of patients with advanced renal cell cancer, advanced neuroendocrine tumours, and hormone receptor-positive advanced breast cancer.

Type of Application and aspects on development

The purpose of the line extension was to add the new dose strength of 1mg dispersible tablets.

No scientific advice was given by EMA or by Member States for this medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as dispersible tablet containing 1 mg of everolimus as active substance.

Other ingredients are: butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone type A, mannitol, cellulose microcrystalline, and silica colloidal anhydrous

The product is available in aluminium/polyamide/aluminium/PVC blister as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used to manufacture the new strength: 1 mg dispersible tablet is the same as that used in the manufacture of the currently authorised Votubia 2.5, 5 and 10 mg tablets, and 2, 3 and 5 mg dispersible tablets (EU/1/11/710/001-015).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Everolimus 1mg dispersible tablets are white to slightly yellowish, round, flat tablets with bevelled edges, no score. The surface is smooth, engraved with “D1” on one side and “NVR” on the other side.

The objective of pharmaceutical development was to develop a lower strength of Votubia dispersible tablets for paediatric use, which can be dispersed in water prior to oral administration. These tablets

have the advantage of fast dispersibility and the dispersion can be prepared with only a few millilitres of water, which allows for convenient administration e.g. by administering the dispersed product directly into the mouth using a syringe.
Everolimus is hydrophobic, practically insoluble in water, soluble in organic solvents, and chemically unstable at temperatures above room temperature, and furthermore sensitive to light. During development, butylhydroxytoluene (BHT) was selected as an antioxidant for stabilization of the active substance.

Votubia 1 mg dispersible tablets are of the same qualitative composition as the already authorised Votubia 2 mg, 3 mg and 5 mg dispersible tablets and therefore no additional excipient compatibility studies were performed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation development of the 1 mg dispersible tablets was based on the well-established formulation and robust manufacturing process of the already authorised 2 mg, 3 mg and 5 mg dispersible tablets. The 1 mg dispersible tablets are manufactured using the same solid dispersion (pharmaceutical intermediate) with the same drug load as registered for the other dispersible tablets.

The dissolution method selected is the same as that authorised for Votubia 2 mg, 3 mg and 5 mg dispersible tablets. Based on experiments performed to develop Votubia dispersible tablets, the discriminatory power of the dissolution method has been demonstrated.

No bioequivalence study has been presented for this line extension application. To support the strength biowaiver request for the proposed Votubia 1 mg dispersible tablets, comparative dissolution data have been provided between Votubia 1 mg dispersible tablets and the authorised 2 mg, and 5 mg presentations. The similarity to the 3 mg dosage strength is covered by the bracketing of the data from the 2 mg and 5 mg strengths. The bracketing is justified due to the same qualitative and proportional quantitative composition of all strengths of Votubia dispersible tablets that vary only in the tablet weight. Votubia 1mg dispersible tablets are intended to be dispersed in water prior to administration. Compatibility studies were performed with dispersions of either 1 x 1mg or 5 x 1mg dispersible tablets using the following administration devices: 10 mL oral plastic syringes, and a 25 or 50 mL transparent glass beaker. These scenarios represent the lowest and highest paediatric dose which requires an administration tool.
No leachable or extractable could be detected. Everolimus 1mg dispersible tablets dispersed in water can be kept for 30 min in plastic syringe and for up to 60 min in glass beaker, prior to administration. Based on the data presented, it was successfully demonstrated that the administration devices proposed in the product labelling are compatible with the suspension.
The same manufacturing process as the authorised higher strengths has been adopted for the proposed strength. The criticality of the process steps and parameters has been assessed and none of the steps and corresponding process parameters are considered critical when maintained within their operational ranges.The primary packaging is aluminium/polyamide/aluminium/PVC blister as the already authorized strengths. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacture of Votubia 1 mg dispersible tablets is a two-step process. The first step involves the preparation of the solid dispersion of the active substance, which is known as the “pharmaceutical

intermediate". The solid dispersion is subsequently processed in the second step with other excipients to obtain the common blend for the manufacture of the finished product.
The manufacturing of the active substance solid dispersion and the common blend is identical to the currently registered manufacturing process for the higher strengths.
The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies, on three consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), mean mass (Ph. Eur.), disintegration time (Ph. Eur.), fineness of dispersion (Ph. Eur.), identity (UV, HPLC), identity of antioxidant, BHT (GC), water (KF), degradation products (HPLC), assay (HPLC), assay of antioxidant (GC), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), and microbial enumeration tests (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 6 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, mean mass, disintegration time, fineness of dispersion, identification, identification of BHT, degradation product, assay, assay of BHT, dissolution, uniformity of dosage, and microbial enumeration test. The analytical procedures used are stability indicating.

During long term and accelerated stability conditions no significant changes have been observed.

The photostability testing was performed on one batch of unpacked product according to the ICH guidelines for the 'Photostability testing of new active substances and medicinal products'. In addition, photostability study with two different levels of reduced light exposure was also performed due to the light sensitivity of the active ingredient. These results indicate that the active substance is sensitive to light and that the corresponding finished product needs to be protected from light.

A complete analysis (chemical and physical testing) was performed on one batch stored for 4 complete freeze and thaw cycles of -20°C/ambient RH for 6 days followed by 1 day at 25°C/60% RH. Samples were taken after 28 days and analysed. No significant changes have been observed.

Based on available stability data, the proposed shelf-life of 24 months without any special temperature storage conditions, and store in the original package in order to protect from light and moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

No applicable

2.3. Non-clinical aspects

No new non-clinical data were submitted in support of this application which is considered acceptable.

2.3.1. Ecotoxicity / environmental risk assessment

The target disease indication in the current line extension applications has not changed, and the addition of a lower strength to the available presentations of Votubia dispersible tablets is not expected to result in an increase in the environmental exposure. The MAH's justification for not providing an updated ERA is considered acceptable.

2.3.2. Discussion on non-clinical aspects

No new data were submitted as part of this application which is considered acceptable considering the scope of this procedure. Any unused medicinal product or waste material should be disposed of in accordance with local requirements as already mentioned in the current wording of the SmPC, section 6.6.

2.3.3. Conclusion on the non-clinical aspects

There is no objection for an approval from non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

No clinical data was submitted as part of this application for the line extension of Votubia 1 mg dispersible tablets. The dose strengths of 2 mg, 3 mg and 5 mg Votubia dispersible tablets were approved in 2013. The therapeutic indications applied for Votubia 1 mg dispersible tablets are the same as those already approved for the higher dose strengths of Votubia dispersible tablets.

Biowaiver:

The “Guideline on the investigation of bioequivalence” indicates that the following criteria should be met to conclude on biowaiver:

a) The pharmaceutical products are manufactured by the same manufacturing process:

The manufacturing processes of Votubia 1 mg dispersible tablets and Votubia 2 mg, 3 mg and 5 mg dispersible tablets are identical.

b) The qualitative composition of the different strengths is the same:

Votubia 1 mg, 2 mg, 3 mg and 5 mg dispersible tablets have the same composition and contain the same drug substance (everolimus) and inactive ingredients.

c) The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

A comparative table of the quantitative compositions of Votubia 1 mg, 2 mg, 3 mg and 5 mg dispersible tablets is provided below.

Table 1: Composition of Votubia 1 mg, 2 mg, 3 mg and 5 mg dispersible tablets

Ingredients	Amount per 1 mg dispersible tablet (mg)	Amount per 2 mg dispersible tablet (mg)	Amount per 3 mg dispersible tablet (mg)	Amount per 5 mg dispersible tablet (mg)
Everolimus n BHT[1]	1.00	2.00	3.00	5.00
Mannitol	54.00	108.00	162.00	270.00
Cellulose microcrystalline / Microcrystalline cellulose	31.25	62.50	93.75	156.25
Crospovidone (Type A)	25.00	50.00	75.00	125.00
Hypromellose (Type 2910)	9.00	18.00	27.00	45.00
Magnesium stearate[2]	2.50	5.00	7.50	12.50
Silica colloidal anhydrous / Colloidal silicon dioxide	1.25	2.50	3.75	6.25
Lactose monohydrate	0.98	1.96	2.94	4.90
Butylhydroxytoluene / Butylated hydroxytoluene	0.02	0.04	0.06	0.10
Ethanol anhydrous /Dehydrated alcohol[3]	-	-	-	-
Acetone[3]	-	-	-	-
Nitrogen[4]	-	-	-	-
Total weight of tablet	**125.00**	**250.00**	**375.00**	**625.00**

[1] Corresponding to everolimus drug substance stabilized with 0.2 % butylhydroxytoluene
[2] Vegetable origin
[3] Removed during processing
[4] Processing aid

d) Appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing:

The in-vitro dissolution profiles of Votubia 1 mg dispersible tablets have been investigated versus the approved Votubia 2 mg and 5 mg dispersible tablets and were considered to be similar (see Quality section).

Everolimus dose linearity in pharmacokinetics

Everolimus is rapidly absorbed after oral administration of the 5-mg everolimus market formulation (MF) tablet with a median tmax of 1-2 hours post-dose. The AUC at steady-state is dose-proportional over the dose range of 5-70 mg in the weekly regimen and 5-10 mg in the daily regimen. Peak blood concentration (Cmax) is dose-proportional between 5-10 mg but increased less than dose-proportionally at weekly doses of 20 mg and higher. There was a significant correlation between area under the concentration-time curve in a dosing interval (AUC0-τ) at steady-state and pre-dose trough concentration (Cmin) in the daily regimen.

The Votubia dispersible tablets are authorised in two indications: subependymal giant cell astrocytoma associated with tuberous sclerosis complex (TSC) based on the results of Studies C2485 and M2301, and refractory partial-onset seizures associated with TSC based on the results of Study M2304.

Results of the dose-proportionality analysis in Study C2485 showed that within individual patients Cmin was proportional with dose ranging from 2.0-10.5 mg/m2 using the MF tablets.

Dose-proportionality analyses of everolimus in Study M2301 were based primarily on intra-subject data and data of patients of different age ranges (<10 years and ≥ 10 years) using 5 years of data in patients with TSC who have SEGA. Results indicate that, in general, everolimus Cmin and C2h were dose-proportional within the dose range tested in study M2301 (1.2 mg/m2-14.7 mg/m2 and 1.1 mg/m2-14.7 mg/m2, respectively using the MF).

In Study M2304, trends indicating increases in Cmin with increasing dose were evident for patients in all age ranges. Results of a modified power model adjusted by age ranges indicated that Cmin was slightly less than proportional in the dose range of 2-32 mg with a slope (90% CI) of 0.827 (0.775, 0.878).

The above data indicate that everolimus has dose-linear pharmacokinetics.

In addition, the bioequivalence between the tablets, dispersible tablets and among the different strengths was evaluated in several studies (C2119, X2105, X2106 and X2111) previously submitted by the MAH.

2.4.2. Discussion and conclusion on clinical aspects

No clinical data were submitted to support this application. During the procedure, the MAH was requested to provide adequate justification for the 1 mg dispersible tablet in line with the requirements of the EMA Bioequivalence guideline for granting a strength biowaiver (i.e., manufactured by the same manufacturing process, same qualitative composition, quantitatively proportional and similar dissolution)

The responses provided adequate and sufficient data regarding manufacturing, dissolution, dose-linear pharmacokinetics and previous bioequivalence studies. Accordingly, a biowaiver for not performing an additional bioequivalence study with the new dose strength can be granted.

2.4.3. PSUR cycle

The PSUR cycle remains unchanged.

2.5. Risk Management Plan

No RMP was submitted in this procedure.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

2.7. Product information

The product information has been updated to reflect the new strength. In addition, QRD changes have been implemented throughout the PI including a clarification of the target population for the SEGA associated with TSC indication (adult and paediatric patients) in section 4.1 of the SmPC.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as no significant changes are made to the PL of the already authorised dispersible tablets.

3. Benefit-Risk Balance

The dose strengths of 2mg, 3mg and 5mg Votubia dispersible tablets were authorised in 2013. The therapeutic indications applied for Votubia 1mg dispersible tablets are the same as those already authorised for the higher dose strengths of Votubia dispersible tablets.

Adequate justification in line with the EMA Bioequivalence guideline has been provided not to perform a new bioequivalence study and grant a strength biowaiver for the proposed 1mg Votubia dispersible tablet.

A positive benefit/risk balance is agreed.

3.1. Conclusions

The overall B/R of Votubia is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Votubia 1 mg dispersible tablet, is favourable in the following indication:

Refractory seizures associated with tuberous sclerosis complex (TSC)
Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC).
Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)
Votubia is indicated for the treatment of adult and paediatric patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.
The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Votubia subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0003/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.