London, 23 November 2011
EMA/40740/2012

Assessment Report

Sumatriptan Galpharm 50 mg Tablets

International non proprietary name: sumatriptan

Procedure No. EMEA/H/C/002140

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

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1 Background information on the procedure

1.1 Submission of the dossier

The applicant Galpharm Healthcare Ltd. submitted on 31 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sumatriptan Galpharm 50 mg Tablets, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2007. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in UK on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83 EC.

The applicant applied for the following indication: "Acute relief of migraine attacks, with or without aura. Sumatriptan Galpharm should only be used where there is a clear diagnosis of migraine.."

The legal basis for this application refers to:

A - Centralised / Article 10(1) / Generic application.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Imigran and appropriate non-clinical and clinical data in support of the change of classification to non-prescription.

Information on Paediatric requirements

Not applicable

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Imigran 50 mg tablets, 50 mg sumatriptan film-coated tablets
- Marketing authorisation holder: GlaxoSmithKline, UK
- Date of authorisation: 24 June1994
- Marketing authorisation granted by:
  - Member State (EEA) : UK
    - National procedure
  - Marketing authorisation number: PL 10949/0222

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form: Imigran 50 mg Tablets

- Marketing authorisation holder: GlaxoSmithKline, UK
- Date of authorisation: 24 June 1994
- Marketing authorisation granted by:
  - Member State (EEA) : UK
    - National procedure
  - Marketing authorisation number: PL 10949/0222

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form: Imigran 100mg tablets

- Marketing authorisation holder: GlaxoSmithKline, UK
- Date of authorisation: 01 August 1994
- Marketing authorisation granted by:
  - Member State (EEA) : UK
    - National procedure
  - Marketing authorisation number(s): PL 10949/0231
- Bioavailability study number: 10-12-072

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Galpharm Migraine Recovery 50mg Tablets has been given a Marketing Authorisation in the United Kingdom on 12 May 2010.

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

Rapporteur: **Barbara van Zwieten-Boot**

Co-Rapporteur: **Robert James Hemmings**

- The application was received by the EMA on 31 March 2010.
- The procedure started on 23 June 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010.
- During the meeting on 18-21 October 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 October 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 February 2011.
- The summary report of the GCP inspection carried out between 17-21 January 2011 at the following site: Sitec Labs Pvt. Ltd. (India) (formerly Medlar Laboratories Pvt. Ltd.) was issued on 10 February 2011.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 March 2011.
- During the CHMP meeting on 11-14 April 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 May 2011.
- During the CHMP meeting on 20-23 June 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 18-21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Sumatriptan Galpharm 50 mg Tablets on 21 July 2011.

1.2 Steps taken for the re-examination of the product

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

Rapporteur: **Tomas Salmonson**

Co-Rapporteur: **George Aislaitner**

- Galpharm Healthcare Ltd. submitted a written notice to the EMA on 29 July 2011 to request a re-examination of the Opinion.
- On 22 September 2011 the detailed grounds for the re-examination request were submitted to the EMA (Appendix).
- The re-examination procedure started on 23 September 2011.
- A Scientific Advisory Group was consulted on 27 October 2011.
- During the CHMP meeting of 14-17 November 2011, the applicant gave an oral explanation before the CHMP on 14 November 2011.
- During the meeting on 14-17 November 2011, the CHMP confirmed a negative opinion for granting a Marketing Authorisation to Sumatriptan Galpharm 50 mg Tablets on 17 November 2011.

2 Scientific discussion

2.1 Introduction

A Centralised Procedure is followed for the proposed product Sumatriptan Galpharm 50 mg, film-coated tablets. The product is indicated for the acute relief of migraine attacks, with or without aura. The recommended dose is a single 50 mg tablet, and 100 mg is the maximum daily dose.

The applicant Galpharm Healthcare Ltd. submitted on 31 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sumatriptan Galpharm 50 mg Tablets, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility was based on demonstration of interest of patients at Community level in view of the availability as non-prescription product in only two member states.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to the reference product Imigran, 50 mg, tablets which is indicated for acute relief of migraine attacks, with or without aura.

Sumatriptan is a selective 5-HT_1 agonist indicated in acute treatment of migraine with or without aura. It is one of a number of selective 5-HT_1 agonists.

2.2 Quality aspects

2.2.1 Introduction

Sumatriptan Galpharm 50 mg has been developed as immediate release film-coated tablets.

The active substance Sumatriptan succinate is described in the Ph.Eur.

The excipients used in the formulation include: mannitol, croscarmellose sodium, hydroxypropylmethylcellulose, purified water, microcrystalline cellulose, magnesium stearate. For the film-coating were used: Opaglos 6000 and isopropyl alcohol.

All the excipients are compendial and for the film-coating agent Opaglos, each individual ingredient is compendial.

The tablets are packed in PolyVinylChloride (PVC)/ Aclar-Aluminium blisters.

2.2.2 Active Substance

The active substance sumatriptan (INN) existing as Sumatriptan succinate or 3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]-N-Methyl methane sulphonamide hydrogen butanedioate is described in the Ph. Eur.

It exists as a white to almost white powder, and Sumatriptan exhibits polymorphism (form I and form II) but the ASMF holder has been manufacturing consistently the polymorphic form I. General physico-chemical properties such as solubility (freely soluble in water and alcohol), particle size and tapped density have been adequately detailed.

An Active Substance Master File Procedure was provided for sumatriptan.

The structure of sumatriptan has been satisfactorily demonstrated by Infra-Red Spectroscopy (FTIR), mass spectrometry, Gas Chromatography coupled with Mass Spectrometry (GC-MS) and Nuclear Magnetic Resonance (^{1}H NMR). In addition Polymorphic form-I has been demonstrated by X-ray diffractometry (XRD) and Differential Scanning Calorimetry (DSC).

A comprehensive discussion on related substances including organic impurities, inorganic impurities, residual solvents was presented. The organic impurities correspond to the impurities listed in the Ph Eur monograph.

Manufacture

A flow diagram of the synthesis was presented and the synthetic route consists of two chemical steps and purification steps.

Information on the manufacturing process was provided in the restricted part of the ASMF..

Specification

The active substance specification is in accordance with the Ph Eur monograph with additions of in-house specifications.

Specification applied by the ASMF holder and the applicant included the following parameters: appearance, solubility, identification (IR), pH (Ph.Eur), absorbance (Ph.Eur.), related substances (Ph.Eur.), water content (Ph.Eur.), sulphated ash (Ph.Eur.) and assay (Ph.Eur.) and additional in-house tests : polymorph identification (X-Ray and DSC), residual solvents (GC), particle size (laser diffraction method), succinic acid content (potentiometry), tapped density (in-house method) and heavy metals (in-house method)

For the parameters specified as per the Ph Eur monograph for sumatriptan, the limits are in accordance with the monograph.. The specification has been adequately justified.

Analytical methods for control are compendial methods in accordance with the Ph Eur monograph with the exception of the test for residual solvents, polymorph identity, particle size and succinic acid content. The methods have been sufficiently outlined. The methods for solubility, identification (IR, XRPD & DSC), pH, absorbance, water content, sulphated ash and heavy metals are standard analytical methods which do not require validation. Assay and related impurities are determined using the compendial methods outlined in the Ph Eur monograph and although not required, the methods have been validated. Also the in-house methods for succinic acid content, residual solvents and particle sizing have been validated.

Certificates of analysis have been provided by the ASMF and the finished product manufacturer for the same five batches of sumatriptan batches of sumatriptan. The results conform to the active substance specifications.

The active substance is packed in virgin foodgrade double polyethylene (PE) bags (inner transparent & outer black) placed in a fiber drum. The polyethylene bags are individually sealed using a plastic fastener and a cellophane tape. Adequate specification including dimensions and IR identification and certificate of analysis are presented for the different packaging materials.

The primary packaging material (PE) is in accordance with the requirements from EU Directive 2002/72/EC as amended and the Guideline on Plastic Immediate Materials CPMP/QWP/4359/03, and Ph. Eur. 3.1.1 Polyolefines.

Stability

Five production batches have been placed under ICH long-term and accelerated conditions (results available for the first three batches up to 72 months at 25C/65 % RH and 6 months at 40C/75% RH). The active substance was kept in the commercial packaging.

Samples were tested for the following stability indicating parameters: description, identification, pH, water content, related impurities and assay.

Forced degradation studies were also conducted under various conditions (high temperature, acidic, basic ,light exposure, oxidative conditions). The active substance was found to degrade under acidic, basic, oxidative and light conditions.

Based on these results the proposed re-test period can be accepted.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The aim of formulation development was to develop a tablet dosage form that would be essentially similar to the reference medicinal product. The formulation development of Sumatriptan Galpharm 50 mg tablets has been adequately described.

The pharmaceutical development was satisfactorily detailed. The parameters investigated for the active substance were appearance, melting range, tapped density, pH, particle size and polymorphism.

The excipients used for the core-tablets are: mannitol (diluent), croscarmellose sodium (disintegrant), hydroxypropylmethylcellulose (binder), purified water (vehicle), microcrystalline cellulose (diluent), magnesium stearate (lubricant). For the film-coating were used: Opaglos 6000 (the qualitative and quantitative composition were provided) and isopropyl alcohol (vehicle).

All the excipients are compendial and for the film-coating agent Opaglos, each ingredient is described in a Pharmacopoiea.

The excipients are commonly used for this pharmaceutical form. The concentrations are usual for an immediate release tablet formulation and can be considered safe in the proposed concentrations.

Following identification of excipients in the reference product, compatibility of admixtures of the active substance and respective excipients was investigated.

Following the choice of excipients on basis of composition of the reference medicinal product and excipient/active substance compatibility study, the quantitative composition was optimised by manufacture and assessment of trial formulations using the preferred process of wet granulation method.

Comparative physico-chemical characterisation with the reference medicinal product was performed.

Comparative dissolution profiles are presented for two batches and the reference medicinal product in three media across the physiological pH range Justification for choice of water as dissolution medium was provided and the justification was considered acceptable. The bio-availability of the active substance is not limited by dissolution. The selected particle size profile of the active substance together with the rapidly disintegrating tablet formulation developed have demonstrated that resulting tablet dissolution rates obtained will not affect the performance of the drug product.

The finished product is packed in PVC/ Aclar-Alu blisters. The PVC/Aclar packaging consists of clear, non toxic, transparent, well thermoformable PVC / PCTFE (Poly Chloro Tri Fluro ethylene) film. The Alu film consists of plain lidding foil (alu foil 20 µm), with heat seal coating. The materials are in accordance with Directive 2002/72/EC. Adequate specifications are provided for the packaging materials including IR identification tests.

Adventitious agents

None of the excipients is of human or animal origin with the exception of magnesium stearate as well as beeswax and shellac (components of the coating mixture).

Magnesium Stearate is of animal origin and the supplier holds an up to date TSE Certificate of Suitability R1-CEP 2000-176-Rev 01, dated 15 November 2006. Shellac and beeswax are derived from insects and are not considered specific TSE risk materials.

Manufacture of the product

The manufacturing process includes dispensing raw materials, sifting the ingredients of the pre-mix, preparation of the binder solution, mixing - granulation & drying, sizing of the granules, blending & lubrication of the granules, compression and film-coating of the tablets. The manufacturing process has been validated for three full-scale baches by a number of studies for the major steps of the manufacturing process.

The batch analysis data show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product Specification

The release and end of shelf-life finished product specification includes the following parameters: description (visual), identification (HPLC and UV), average weight, uniformity of dosage units (PhEur. 2.9.40), water content (Karl-Fisher), dissolution, assay (HPLC), related substances (HPLC), residual solvents (HPLC), microbial contamination (PhEur)

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies were conducted on three pilot batches and three commercial scale batches under ICH long-term conditions (up to 36 months at 25°C/60% RH) and accelerated conditions (6 months at 40°C/75% RH). The stability batches were kept in the commercial packaging (PVC/Alu blisters).

The same limits are applied at shelf life as for release testing with the exception of water content. Residual solvents are controlled in process and the limits are well within the ICH permitted daily exposure limits.

For each tablets, the following parameters were tested: description, water content, dissolution, related substances, assay and microbial contamination (tested initially and at the end of shelf life).

Analytical procedures are identical to those applied at release..

Also, the test on microbial contamination was performed after 36 months on one batch showing the results meeting the set requirements.

A photo-degradation study was performed on one batch according to the ICH Guideline. Based on the stability data, the tablets are not sensitive to light and no additional corresponding storage is required.

Based on the available long-term and accelerated stability data, the shelf-life and storage conditions as proposed can be supported.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Satisfactory information has been provided for the development, manufacture and control of the active substance sumatriptan and for the finished product. . The manufacturing process is a conventional process for the film-coated tablets and the stability has been adequately tested and demonstrated in accordance with ICH guidelines. The results of the 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 the clinic.

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 SPC. 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 TSE safety. There are no unresolved quality issues which might have negative impact on the benefit/risk balance

2.3 Non- Clinical aspects

2.3.1 Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SPC are in line with the SPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies were required.

2.3.2 Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Sumatriptan Galpharm 50 mg tablets manufactured by Galpharm based on the anticipation that the bulk of the usage of this product will be by patients who have switched from a prescription source which is expected to represent a very small fraction of the overall usage of

Sumatriptan. Therefore it is considered unlikely to result in any significant increase in the combined sales volumes for all sumatriptan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for sumatriptan 50 mg tablets.

For the clinical assessment, *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 is* of particular relevance.

The CHMP requested a GCP inspection for the bioequivalence study (03-115) initially submitted to support the application. The inspection revealed that the trial was not conducted in compliance with GCP and therefore the submitted data could not be considered supportive for the Marketing Authorization Application.

A new bioequivalence trial (study 10-12-072) was submitted in support of the application. This study was pivotal for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of sumatriptan based on published literature.

Exemption

Not applicable

Clinical studies

No new clinical studies were performed. To support the application, the applicant originally submitted one single-dose bioequivalence study (03-115). This bioequivalence study initially referred to by the Applicant was rejected due to several identified irregularities. An inspection revealed that the clinical study was not conducted in compliance with GCP and therefore the submitted data could not be considered supportive for the Marketing Authorization Application.

Taking these findings into account, the applicant applied for a BCS-based biowaiver. However, the generic product contained different excipients and even a critical excipient (mannitol), known to have a potential to affect GI transit and absorption, as compared to the innovator. Additionally, for other excipients the quantitative composition was also not similar. Hence the CHMP considered that this generic did not fulfil the requirements set in the Guideline on Investigation of Bioequivalence, Appendix III Biowaiver, for class III drugs (i.e. excipients that might affect bioavailability (e.g. sorbitol, mannitol) should be qualitatively and quantitatively the same and other excipients should be qualitatively the same and quantitatively very similar). As it could not be ruled out that absorption of sumatriptan from the generic formulation may be different from that of the innovator formulation, a BCS-based biowaiver could not be granted.

In response, the applicant first submitted an interim report of a new bioequivalence study (10-12-072) performed by the same CRO, and subsequently the results of this new bioequivalence study, which is assessed below.

2.4.2 Pharmacokinetics

Pharmacokinetic study 10-12-072

Study 10-12-072 was a randomized, two-treatment, two-period, two-sequence, cross-over bioavailability study in 28 healthy human subjects under fasting conditions. This study was performed between 5 April and 28 April 2011. Bio-analysis and statistical analyses were completed on 4 May 2011. Clinical and bio-analytical unit was Sitec Labs Pvt. Ltd, Mumbai, India.

Sumatriptan 100mg tablet of test or reference product was orally administered as a single dose with 240 ml of water after an overnight fast of at least 10 hours in each period. Water was not allowed from 1 hour pre-dose and till 2 hours post-dose. Blood samples were drawn pre-dose and at 0.17, 0.33, 0.50, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, and 24.00 hours post-dose. Wash-out period was at least one week.

Samples were collected through an indwelling cannula placed in a forearm vein till 12.00 hours post-dose samples. 24.00 hours post-dose sample was collected via direct venipuncture. Blood samples were collected after discarding the first 1 ml. The blood samples were collected in 5ml vacutainers containing heparin as an anticoagulant. Samples were centrifuged at 8°C - 10°C and 2500 - 3000 rpm for 10 minutes. Plasma was separated and placed in suitable stopper tubes. All plasma samples were stored upright below -70°C until the analysis of the samples.

The study protocol was approved by an independent ethics committee on 24 January 2011.

The CHMP considered that the design of the study was acceptable. The sampling schedule was adequate to estimate PK parameters and the wash-out period is long enough to avoid carry-over effect. Indeed, there were no positive pre-dose samples in the second period.

A statement of completeness of the report was signed by the investigators 10 June 2011. A QA statement and which parts of the study were audited were submitted. There were no protocol violations reported, only a few deviations for the timing of blood samples were noted. These deviations were considered by the CHMP to have no consequence for the conclusions of the study.

Test and reference products

Test product: Sumatriptan 100 mg tablet (of Cipla Ltd., India), batch G05936, manufacturing date 12/2010. Potency 99.5%

Reference product: Imigran tablet (Sumatriptan 100 mg of Glaxo Wellcome, UK), batch PJ1363, expiration date 8/2013. Potency 98.4%

Population(s) studied: Twenty-eight (28) healthy male volunteers with a mean age of 25 years were randomized. Twenty-two (22) subjects completed the study according to protocol. Four subjects were withdrawn because of AEs; one subject did not show up for the second period and the cannule could not be introduced. All subjects who completed the study were included in the pharmacokinetic and statistical analysis. The study population was acceptable to the CHMP.

Analytical methods

The plasma samples were analyzed by a validated LC-MS/MS method. The method validation was performed in human plasma in the linear range of 0.5 to 200 ng/ml. A cross validation was conducted to validate the procedure from human plasma harvested using sodium heparin plasma. Specificity and selectivity, precision, accuracy, recovery, stability and matrix effects met the acceptance criteria.

Incurred sample reanalysis was performed on 161 of the 1033 analysed samples. The % difference in concentrations obtained from the incurred samples from their initial concentration was >20% in 4 out of 161 samples. The percentage of samples within acceptance criteria for sumatriptan was 97.5%.

Pharmacokinetic Variables & Statistical methods

The primary pharmacokinetic variables were C_{max}, AUC_{0-t} and AUC_{0-inf} and the secondary variables were T_{max}, K_{el} and $T_{1/2.}$

Analysis of variance (ANOVA) was performed (α=0.05) on the untransformed and log (ln)-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf}. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors.

90% confidence intervals for the difference between treatment, least-square means (LSM) were calculated for both untransformed and log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf}. To be considered bioequivalent, ratios & CI should lie between acceptance range of 80-125%.

The CHMP considered that pharmacokinetic parameter calculation and statistical methods to be acceptable.

Results

Results are summarized in the table and figure below.

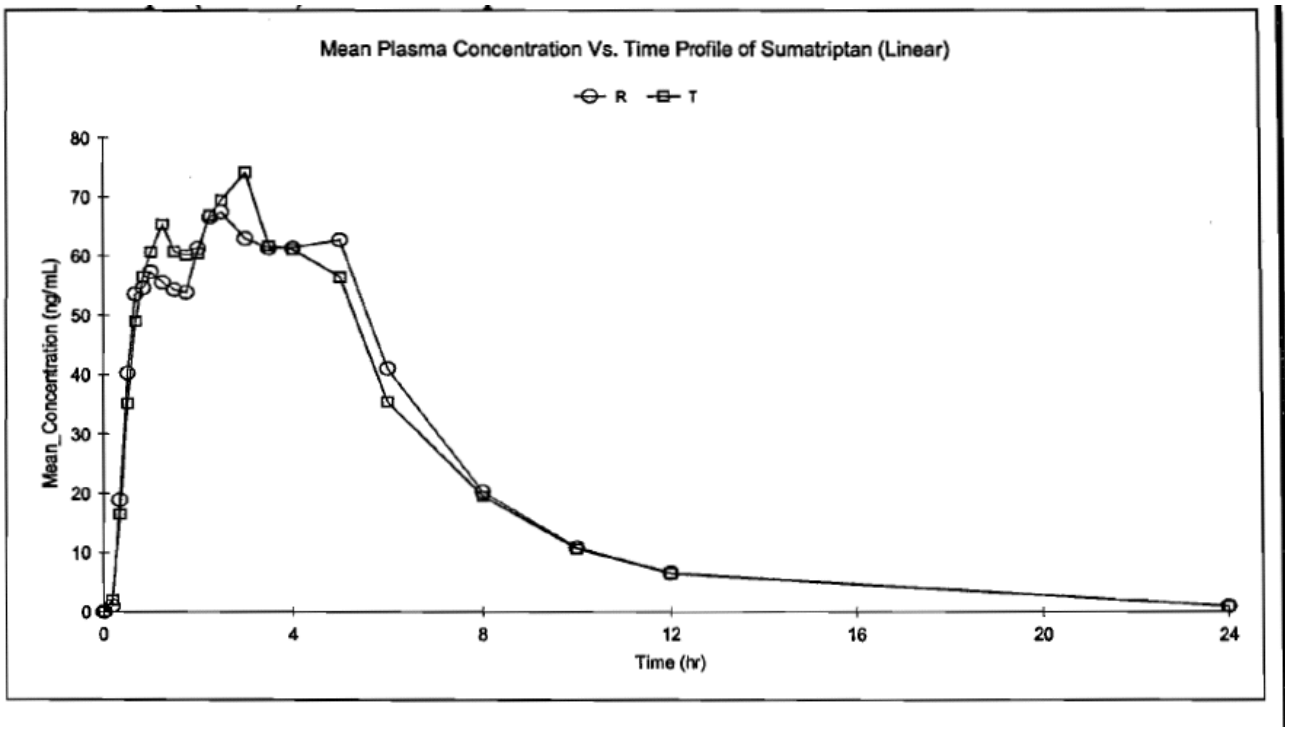
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) of study 10-12-072 (N=22)

Treatment	AUC_{0-t} ng/ml/h	AUC_{0-inf} ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	476 ± 104	485 ± 104	97.5 ± 28.6	2.75 (0.50-5.00)	4.1 ± 1.3
Reference	480 ± 132	491 ± 130	95.6 ± 29.4	2.39 (0.67-6.00)	4.5 ± 1.8
*Ratio (90% CI)	100.4 93.3-108.1	99.9 93.3-107.0	101.5 85.6-120.4		
CV%	14.2	13.2	33.6		

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$T_{1/2}$ half-life

*ln-transformed values

Figure 1. Mean concentrations of sumatriptan [ng/mL] vs. time [h] (study 10-12-072, N=22)



AUC_{0-t} covered >90% of AUC_{0-inf} in all subjects. Sequence, formulation and period effect were not significant for any primary PK parameter. No pre-dose concentrations were observed. Coefficient of variation for C_{max}, AUC_{0-t} and AUC_{0-inf} was similar between the Test and Reference product.

Safety

There were 19 AEs in 11 subjects following test product and 11 AEs in 8 subjects following reference product. 14/28 subjects experienced an AE in the first period only 5/24 experienced AE in the second period. No serious adverse events were reported.

The CHMP considered that the results of study 10-12-072 indicate that sumatriptan 100 mg tablets manufactured by Cipla, India are bioequivalent with Imigran sumatriptan 100mg tablets, GlaxoSmithKline UK under fasting conditions as the 90% CI for AUCt, AUCinf and Cmax were within the acceptance range of 0.80-1.25.

The CHMP noted that the bioequivalence study was performed with a higher strength (100 mg) than marketed (50 mg). In the final response document submitted on 6 July 2011, dissolution tests for the sumatriptan 50 mg and 100 mg tablets used in bioequivalence study 10-12-072 showed rapid dissolution (>85% in 15 min) over the entire pH range. The criteria for a waiver according to *Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98* and its revision were met. Thus, the results of the 100 mg formulation can be extrapolated to the only strength to be authorised, i.e. 50 mg.

Conclusions

Overall, the CHMP considered that the results of the 10-12-072 bioequivalence study indicated that sumatriptan 100 mg tablets manufactured by Cipla, India are bioequivalent with Imigran, sumatriptan 100 mg tablets, GlaxoSmithKline UK under fasting conditions as the 90% CI for AUCt, AUCinf and Cmax were within the acceptance range of 0.80-1.25. These results can be extrapolated to the only strength of sumatriptan applied for as part of this application, i.e. 50 mg. Bioequivalence could therefore be concluded.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Post marketing experience

No post-marketing data related to this particular medicinal product were made available as part of this application.

2.4.5 Discussion on Clinical aspects

Clinical efficacy

The evidence of efficacy of 50 mg sumatriptan is well known and for this application supported by literature submitted by the Applicant. The proposed 50 mg strength is in line with that of the reference product. The strength 100 mg is recommended by the reference product if patients do not get benefit from the 50mg. However, according to recent clinical evidence, doses above 50 mg may not necessarily provide a greater effect. With this application, only 50 mg sumatriptan was applied for.

Clinical safety

The clinical safety of sumatriptan is well-known based on 18 years of clinical experience and wide use. To further substantiate this, the Applicant submitted data from UK Drug Analysis Print (DAP) in module 5 (m5.3.6.) relating to single ingredient sumatriptan products covering the period from 24 June 1994 to 24 August 2009 of a total of 4,805 adverse drug reactions (ADRs) relating to 2,264 ADR reports. Twenty-five fatalities were reported and are listed as: blood disorders (n = 1), cardiac disorders (n = 3) one due to vascular disorder, general disorders (n= 2), injuries (n = 1), neoplasms (n = 2), nervous system disorders (n = 11), psychiatric disorders (n = 1), respiratory disorders (n = 3), overdosage (n

= 1). Specific details of these fatalities and the degree of causal relationship to sumatriptan treatment were not provided.

The most frequently reported adverse reactions are summarised in the table below:

Table 1. Most frequently reported UK adverse drug reactions for sumatriptan during the period 1 January 1994 to 24 August 2009.

Type of adverse reaction	Number of reports
Chest discomfort	233
Paraesthesia	228
Dizziness	213
Chest pain	211
Nausea	198
Headache	140
Dyspnoea	110
Vomiting	87
Palpitations	86
Sensation of heaviness	77
Neck pain	69
Pain in extremity	68
Burning sensation	64
Asthenia	61
Somnolence	57
Fatigue	57
Hypoaesthesia	57
Malaise	55
Feeling abnormal	53

The pattern and relative incidence of these reported ADRs match the known safety profile of sumatriptan in the literature. The majority of these ADRs occurred when sumatriptan was available as prescription medicine with a recommended dose of 100 mg.

A further Drug Analysis Print of the ADRs reported covering the period 4 December 2006 until 30 November 2009 was also provided. In this analysis there were a total of 188 ADRs from 62 reports and no fatality occurred. In the view of the Applicant, the ADRs reported did not reveal significant or untoward safety concerns following the introduction of non-prescription 50 mg sumatriptan. The Applicant concluded that the pattern and relative incidence of the reported common AEs are

comparable to the safety profile of sumatriptan in the literature.

However, difficulties arose with regards to the safety implications linked to the proposed legal status of supply: the CHMP considered that the safety profile of the non-prescriptive 50 mg sumatriptan was difficult to assess as the data were limited. The absolute numbers of reported events are of limited value as there is no denominator (patients' exposure time) and hence the relative incidence was also not assessable. Moreover, the data presented were AEs from a mixed population (i.e. reports of all prescription sumatriptan strengths 25 mg, 50 mg and 100 mg and non-prescriptive prescription combined). It was not possible to compare the data of the prescription status with those of the non-prescription status.

Therefore, no conclusions could be drawn by the CHMP on the safety of non-prescription sumatriptan 50 mg. The safe use in cardiovascular and cerebrovascular compromised subjects had not been addressed. In the absence of data, the CHMP considered that general safety issues could not be excluded.

However, the CHMP needs to make benefit/risk evaluations based on the data submitted and scientific knowledge, taking into account the proposed precautionary measures.

Reference to wide-spread availability of other approved non-prescription treatment options in migraine was only partly accepted as an argument. In view of the Committee a B/R evaluation for non-prescription should always be made taking into account the specific risks of the active substance (i.e. sumatriptan).

These are emphasised by the contra-indications, precautions of use, adverse events as stated in the SPC of sumatriptan. To this effect, some primary and secondary care guidelines concerning migraine place triptans as second line in their treatment recommendations after an insufficient response on an appropriate dosed combination of NSAID/antiemetic, based on the unfavourable safety profile of triptans taking into account the availability of alternative treatment. The CHMP also considered that the intended intensive monitoring programme proposed by the applicant concerning correct diagnosis, first prescription by physician, monitoring of previous responses, correct use, monitoring frequency of use, etc reinforces this view. This high level of monitoring goes against and would violate the principle of patient's self management of non-prescription products.

In addition, this monitoring programme would need to be performed every time a new supply is foreseen, in order to verify whether or not the conditions of a patient have changed. Whether this would occur in practice on a regular basis has not been addressed.

The precautions poorly address the change in patients' migraine characteristics warranting different treatment/migraine-prophylaxis, occurrence of mixed headache, medication overuse, change of medical condition with respect to cardiovascular contra-indications and warnings.

Additionally, the CHMP considered that the risk and burden of medication overuse headache (MOH) due to sumatriptan use should not be underestimated. Overall estimates of MOH prevalence range from 0.7% to 1.7% up to 5%. However, in a study of 532 patients with episodic migraine overall 10% of the patients overused headache medication. Over-users of triptans developed chronic headache faster and used fewer single dosages than over-users of analgesics. In addition, 12% of the patients in this study had a combination of migraine and tension-type headache and the 1-year incidence of chronic headache was 14%. Hence, chronic headache in migraine patient may be due to a prolonged migraine attack, increase of tension type headache or MOH. It may not be easy to detect an early migraine attack amidst chronic headaches in patients with mixed headaches. Hence, an emerging migraine attack might not be easy to distinguish and misclassification leading to sumatriptan overuse is likely. Triptans overuse is becoming the most common cause of MOH. Triptans are more likely to

induce MOH than simple analgesics. It is noted that overuse of analgesics and acute migraine drugs fulfil the criteria of substance abuse disorder in two third of all patients with MOH.

The proposed package size of two tablets does not form a guarantee prevention of medication overuse headache. It is the frequency of acute attacks that determines medication use, not the package size. As such, the small package size is not seen as a sufficient risk minimisation measure.

The Applicant also proposed to strengthen the Package Leaflet and to introduce Pharmacy Training, including a patient migraine questionnaire and an algorithm for managing migraine, to make it clear when non-prescription analgesics may be suitable for the customer and when migraineurs should consult their physician.

The Applicant additionally proposed to conduct a post-approval observational study, to commence at launch, to assess the safety of non-prescription supply. In the view of the Applicant, this study would address the concern for longitudinal follow-up by being conducted over 36 months (with interim reports at 12 and 24) and following individuals for a period of time sufficient to monitor changes in migraineurs. The study would also specifically assess whether sumatriptan or other treatment is more suitable for the patient and whether the first diagnosis and treatment was made by the physician. True and simulated patients would be recruited. The applicant proposed that the continued approval of the MA for sumatriptan would be conditional upon a positive outcome of this study.

The CHMP questioned, however, whether the proposed observational study would adequately evaluate the appropriate use of sumatriptan in practice. The study would be performed in a highly motivated setting which does not evaluate whether in practice the questionnaire is always performed by a qualified pharmacist, longitudinal follow-up is adequate and changes in patient's characteristics are picked up.

2.4.6 Conclusions on clinical aspects

The CHMP considered that the results of the bioequivalence study 10-12-072 indicated that sumatriptan 100 mg tablets manufactured by Cipla, India are bioequivalent with Imigran, sumatriptan 100 mg tablets, GlaxoSmithKline UK under fasting conditions as the 90% CI for AUCt, AUCinf and Cmax were within the acceptance range of 0.80-1.25. These results could be extrapolated to the only strength of sumatriptan applied for with this application, i.e. 50 mg.

However, the CHMP considered that treatment with sumatriptan needs medical diagnosis and follow-up of the patient in particular in view of the danger associated with its significant cardiovascular and cerebrovascular adverse effects.

Even if a patient has been initially prescribed sumatriptan following medical diagnosis, patients may undergo changes in cardiovascular and cerebro-vascular risk over time, as a patient's condition changes. Monitoring is also necessary due to possible change in type of headache, possible medication overuse headache and assessment of the need for prophylactic treatment with other medicines. Therefore, in a Non-Prescription setting, where Sumatriptan would be used without medical supervision and follow-up, this is "*likely to present a danger either directly or indirectly, even if used correctly*", as per the first criterion of the EC 'Guideline on Changing the Classification for the Supply of a Medicinal product for Human Use' (The Rules governing Medicinal Products in the European Community, Volume 2C: Guidelines).

In considering whether this criterion applies, the CHMP took into account the following factors:

Cardiovascular and cerebro-vascular adverse events are major safety concerns with sumatriptan use, as triptans have been shown to cause narrowing of coronary arteries and coronary vasospasm. Cardiovascular and cerebro-vascular risk also changes over time as a patient's condition change. Additionally, the literature shows that adverse cardiovascular events may occur in patients with previously unrecognized cardiovascular disease. Although previous history of cardiovascular and cerebrovascular disease are contraindicated with sumatriptan, if the non-prescription status be granted under the model proposed by the Applicant, the risks deriving from use by these patients would be greater. This is of particular concern with the use of sumatriptan in patients with a previously unrecognized cardiovascular disease as the cardiovascular status/risks may change over time.

The non-prescriptive status implies that the absence of clinical supervision resulting from the change in prescription status can be covered by pharmacists or by patients themselves. The applicant proposed the following restriction to the indication *"….patients who have previously been prescribed sumatriptan 50 mg tablets for their migraine".* However, the applicant did not satisfactorily demonstrate that the addition of this sentence would indeed reduce the risk of inappropriate use of the product when used in the Non-Prescription setting.

Patient's condition and headache/migraine characteristics, response to treatment, co-medications may change over time, potentially affecting the appropriateness of sumatriptan use. Using sumatriptan, for instance, some migraine patients may suffer from more frequent and more severe attacks, requiring intervention from a physician, to review, modify or suspend sumatriptan use as a consequence or to initiate prophylactic treatment with other medicines. Detection of misuse and overuse and corrective action would be delayed if patients would not have to consult a doctor anymore.

The CHMP was of the opinion that the addition of contraindications, warnings and information on the use of interacting drugs to the Sumatriptan Galpharm SPC/PL proposed by the Applicant will not be sufficient to address the concerns in a non-prescription setting. Patients are likely to be unable to evaluate and distinguish between the various contraindications and warnings. Additionally, the CHMP was not convinced that the change in risk for cardiovascular events and migraine status over time could be fully evaluated by patients or pharmacists, thus making sumatriptan unsuitable for the non-prescription setting.

To complement the patient self-assessment, the applicant proposed a Patient Migraine Questionnaire and a Pharmacy Migraine Management algorithm as risk minimization measures. These did not address the concerns and were not considered acceptable as they showed a high level of complexity. Additionally, the pharmacist would have been required to take a general medical history. These measures would be incompatible with the non-prescriptive principle.

It can not be expected that the patient is able to distinguish and evaluate the various contraindications and warnings (i.e. ischemic stroke, TIA, basilar migraine, coronary heart disease, Prinz-Metal angina, uncontrolled (=unknown) hypertension, cardiac risk profile, etc.). Whether or not the degree of cardiac risk can be fully evaluated by patients or pharmacists is questionable.

A large proportion of subjects suffer from mixed headaches, and the differential diagnosis of migraine vs. headache is not straightforward. Without medical supervision, the condition/symptoms may not be correctly assessed. Even with the proposed restriction to be given sumatriptan only further to previous medical diagnosis of migraine by a doctor, this concern was not considered resolved.

Under a non-prescription status, the risk of medication overuse headache (MOH) or misuse can not be controlled. With a non-prescriptive status, any patient who had been previously diagnosed with migraine could, in practice, always obtain and use the medicinal product, increasing the risk of the medication being overused or used incorrectly.

This incorrect use of triptans and risk of medicine induced headache by triptans is not theoretical. There are reports in the literature which indicate that sumatriptan may have a higher risk of overuse than analgesics and leads to medication-overuse headache. In the general population, chronic daily headache has a prevalence of 2% -4% and MOH accounts for 50% of these cases. Triptans are the most frequent drugs taken by patients who develop MOH and have the shortest delay (1.7 years) between drug overuse and onset of daily headache.

The risk and burden of medication overuse headache (MOH) due to sumatriptan use should not be underestimated. Overall estimates of MOH prevalence range from 0.7% to 1.7% up to 5%. However, in a study of 532 patients with episodic migraine the 1-year incidence of chronic headache was 14%. Overall, 10% of the patients overused headache medication. Over-users of triptans developed chronic headache faster and used fewer single dosages that over-users of analgesics. In addition 12% of the patients in the study had a combination of migraine and tension-type headache. Hence, chronic headache in migraine patient may be due to the late migraine attack, tension-type headache or MOH. It may be difficult to detect an early migraine attack amidst chronic headaches in patients with mixed headaches. Thus, an emerging migraine attack with a chronic headache might not be easy to distinguish and misclassification leading to sumatriptan overuse is likely. Triptans overuse is becoming the most common cause of MOH. Triptans are more likely to induce MOH than simple analgesics. Finally, the overuse of analgesics and acute migraine drugs fulfil the criteria of substance abuse disorder in two third of all patients with MOH.

Detection of misuse and overuse and its treatment would be delayed if patients would not have to consult a doctor anymore.

There is wide use and 18 years of clinical experience with the prescription status, while the non-prescription is only approved since 2006 in the UK and since 2008 in Sweden. Thus, the mechanism of action and side-effects of sumatriptan are well-known, whilst the safety profile of non-prescription sumatriptan 50mg (in comparison to the prescription medication sumatriptan) has not appropriately been addressed by the Applicant.

Two reports of Drug Print Analysis (DAP) post-marketing safety data (both from the UK, one covering 1994-2009 and the other 2006-2009), were submitted by the Applicant to support the clinical safety of Non-Prescription sumatriptan. However, these data were limited, and the safety profile of the Non-Prescription sumatriptan 50 mg was not assessable. The absolute numbers of reported adverse events are of very limited value as there is no denominator (i.e. "patient exposure" is not known). More importantly, the data presented are Adverse Events from a mixed population (i.e. reports of all prescription sumatriptan strengths - 25 mg, 50mg and 100mg and 50 mg Non-Prescription combined). Thus, it was not possible to compare the data of the Prescription status with those of the Non-Prescription status. In addition, for the less severe/serious adverse events reporting rates for Non-Prescription product are unreliable (i.e. an increase in incidence may not be picked-up) as it is known that AEs reporting with Non-Prescription products is lower in comparison with those on Prescription. In conclusion, the safety data has not been presented by the Applicant in a way that provided sufficient reassurance over the potential dangers associated with the non-prescription status of sumatriptan.

The data submitted were neither comprehensive nor sufficient. Overall, the safety data was not presented by the Applicant in a way that provided reassurance over the potential dangers associated with the non-prescription status of sumatriptan.

In conclusion, the CHMP considered monitoring to be necessary when using sumatriptan: if patients would not be followed-up by a doctor, the cardiovascular and cerebrovascular risks can not be controlled. Moreover, there is a potential for wide misuse (with the consequence of either medication

overuse headache or missing the need for switching to alternative prophylactic treatment). Therefore the CHMP did not recommend a non-prescriptive status for sumatriptan.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

In addition, the CHMP considered that in the case of a positive opinion the applicant should have taken the following minor points into consideration:

The Applicant was requested to ensure of being in production with the EMA and rapporteurs for electronic submission of ICSRs before registration of the product.

On electronic reporting of ICSRs to the EMA and Rapporteur, the table of SOPs in the DDPS version 004 (dated 4 May 2011) stated that the Applicant is currently in process of conducting E2B testing with the EMA instead of being in production. Note that this would also have required an amendment of SOP 11.0.05. If the CHMP had recommended the granting of the marketing authorisations, the DDPS would have needed an amendment before marketing of the product.

Risk Management Plan

Initially, the Applicant submitted a justification for not submitting a risk management plan (RMP). The Applicant did not expect the change to non-prescription status to result in any additional risk to the patient since non-prescription sumatriptan had been available in the UK since 2006 and safety data indicate no problems. The value of the submitted safety data was, however, questioned as stated in the clinical part of this assessment.

The Applicant further suggested that the proposed labelling, small pack size and the involvement of the pharmacist, on whose vigilance the Applicant heavily relies on, will ensure patient safety. The CHMP, however, noted that the as part of their assessment they had to consider whether for sumatriptan a non-prescription status may be approvable implying how clinical issues that are no longer covered due to the loss of prescription status can be covered by the user.

Despite the Applicant's initial reasoning not to submit a full RMP, the Applicant proposed a number of precautionary steps (see below) in order to thoroughly monitor the safety of this product and to ensure the risk benefit ratio remains favourable.

Scenario	Action	Outcome
Patient has not previously been diagnosed with migraine	SmPC section 4.4 and PIL (section 2. Do not use Sumatriptan Perrigo) states that only patients who have previously been diagnosed with migraine and prescribed sumatriptan should use this product	Patient does not meet the criteria for OTC sumatriptan therefore is not sold the product.
Patient is contraindicated for the product or is concerned with a warning or interaction	Pharmacist directs the patient to their doctor	Patient cannot purchase the product
Patient is concerned with a warnings and/or interaction on the product labeling	Pharmacist directs the patient to their doctor	Patient does not purchase the product
Patient begins to use Sumatriptan 50mg Tablets too frequently and headaches become worse	As specified in the labelling patient is directed to their doctor.	Patient refers to Doctor. Pack size of two tablets minimizes this risk
Patient experiences a listed or unlisted adverse event	Patient Information Leaflet section 4 to contain appropriate contact details for medical information	Patient contacts Perrigo or Healthcare Professional and appropriate information is collated
New adverse event is identified	As per Pharmacovigilance Plan, the new AE would be reported to Perrigo and would be discussed by appropriate personnel with the company. Updates to the labelling and/or risk benefit profile would be reported to EMEA	Adverse event included in the product labelling

The CHMP, however, noted that the above simple precautionary measures proposed by the Applicant would classify as risk minimisation measures and needed therefore to be fully outlined in an RMP. Therefore, they requested that a number of concerns identified during the assessment of the dossier would need to be addressed in a full RMP, aimed especially at the new non-prescription status, with its own specific identified and potential risks.

Additionally, the Applicant was requested to investigate whether their initially proposed risk minimisation measures (e.g. pharmacy educational material) were sufficient to ensure patient safety. Aspects to be taken into account include safety monitoring in PSURs with cases reported from Non-prescription and prescription sales clearly distinguished and separately analysed. Besides this, the Applicant proposed to perform a study to investigate the adherence to the instructions of use in practice, the protocol for which would be part of the RMP.

Thus, the applicant submitted a risk management plan, subsequently amended as assessment of the MAA progressed, which in its latest version (version 3, dated May 2011) included a pharmacy training manual containing key messages, as follows:

Introduction
- Brief description of the:
  - Reason for this training and protocol
  - Objective of the materials
  - Symptoms and incidence of migraine, and the impact on society as well as individuals family and work life

Symptoms
Causes of migraine
Advice for people with migraine
Diagnosis of Migraine
Physician referral criteria
Urgent physician referral criteria
Treatment
- First line
- Second line
- Use of anti-emetics
- Not recommended

Medication overuse
Follow up for change in symptoms, treatment or risk factors
Possible Interactions
Possible side effects

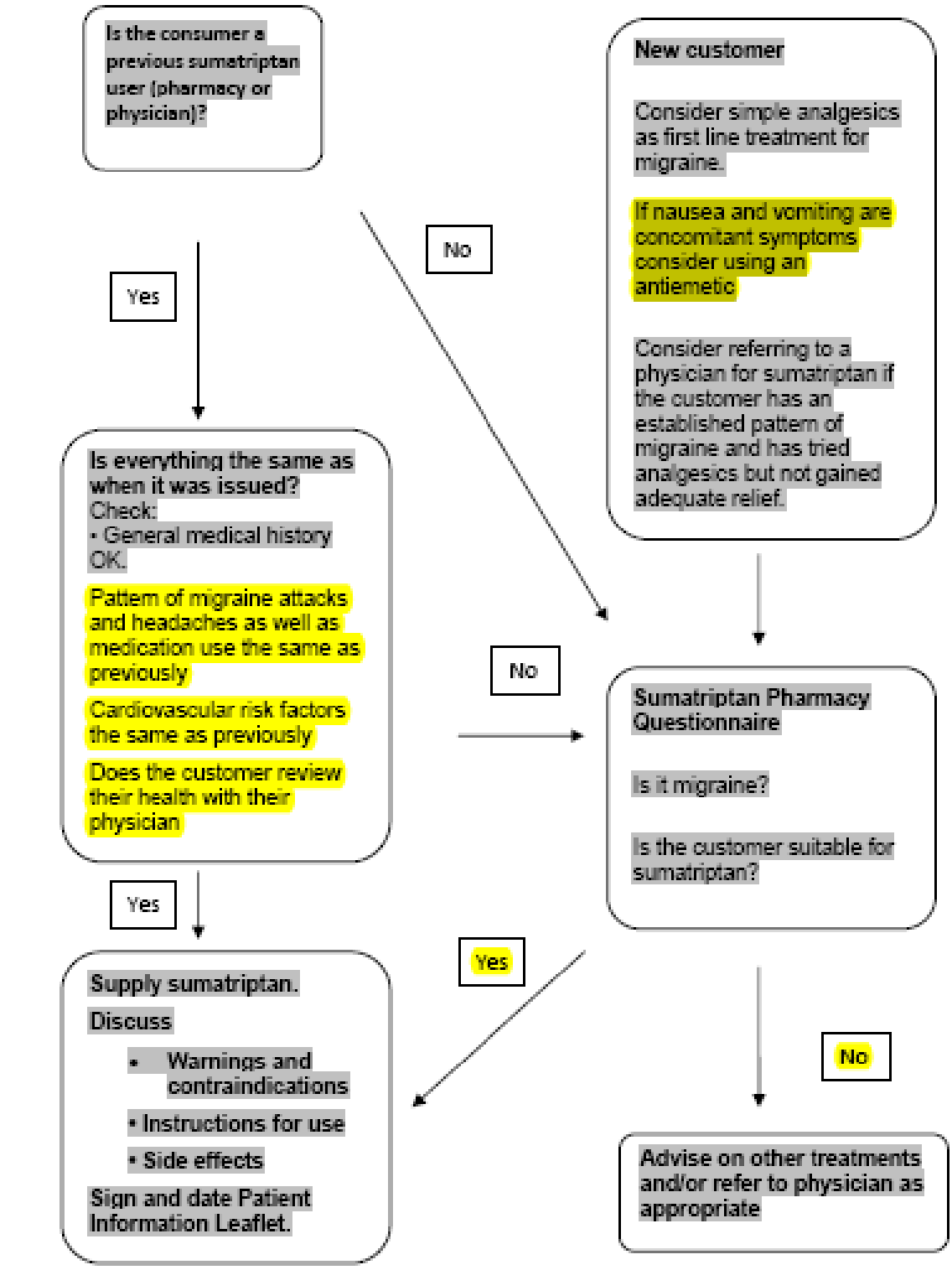
The instructions on the use of the product show the following items:

Instructions on the use of Sumatriptan Galpharm

- BEFORE YOU TAKE SUMATRIPTAN GALPHARM
  - Situations when not to take Sumatriptan Galpharm
  - Special warnings about this medicine
  - Cardiovascular risk assessment
  - Medication overuse
  - Physician review
  - HCP referral criteria
  - Recommendations during pregnancy and breast-feeding
- HOW TO TAKE SUMATRIPTAN GALPHARM
  - Special Warnings whilst taking Sumatriptan Galpharm
  - Further information
  - Overuse headaches
  - Risks associated with migraine
- Sources of further information
- Adverse event reporting

A migraine management algorithm to be taken into account by the dispensing pharmacist was also proposed. This algorithm was subsequently amended to include additional aspects (marked in yellow in the flowchart below):

Pharmacy Migraine Management Algorithm (FLOW CHART)



The proposed RMP also included a 'customer over the counter sumatriptan questionnaire', including a question whether the patient's pattern or frequency of migraines and headache changed as well as a reminder to tell the pharmacist and physician of any changes in the risk factor areas.

The applicant additionally proposed to further develop this document in consultation with primary care pharmacists and physicians before pilot testing it with a controlled group of real and 'primed' pharmacist/ customer migraine consultations. The final document would have had to be tested in a proposed post-marketing study.

The various efforts and amendments to the RMP as outlined above were noted by the CHMP. However, the submitted RMP was not in an acceptable format in line with Volume 9A guidance. Furthermore, it was considered that with respect to off-label use and use in other age groups than currently allowed by the SPC this risk was not adequately addressed.

Having considered the information outlined above, the CHMP still questioned whether the proposals adequately tackled the response on alternative treatment before switching to sumatriptan and whether the risk of migraine medication overuse was sufficiently addressed. To complement the patient self-assessment, the applicant proposed Patient Questionnaire and the Pharmacy Management algorithm as risk minimization measures. These were not considered acceptable as they showed a high level of complexity. Additionally, the pharmacist would have been required to take a general medical history. All these measures would be incompatible with the non-prescriptive principle.

The CHMP, having considered the data submitted in the application was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

In addition, the CHMP considered that the RMP was technically considered invalid due to lack of Safety Specification (no safety concerns were put in relation to the proposed risk minimisation measures).

3 Benefit-Risk Balance

This application concerns a 50 mg sumatriptan tablets. The reference product chosen for bioequivalence, Imigran Tablets 100 mg, is indicated for acute relief of migraine attacks, with or without aura. No non-clinical studies have been provided for this generic application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics nor on the efficacy and safety of the active substance.

The bioequivalence study [10-12-072] forms the pivotal basis with a randomized, two-treatment, two-period, two-sequence, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of [applied product] met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The application contained, however, insufficient data with regards to supply and use. The following aspects are inadequately demonstrated: Safety of the non-prescription status.

4 Recommendation

Based on their review of the data on safety and efficacy, and in line with the provisions of Art. 71 of Directive 2001/83/EC and the EC 'Guideline on Changing the Classification for the Supply of a Medicinal product for Human Use' (The Rules governing Medicinal Products in the European Community, Volume 2C: Guidelines), the CHMP considered that the safety of Sumatriptan Galpharm for the "acute relief of migraine attacks, with or without aura" has not been sufficiently demonstrated for the non-prescription status as detailed in the grounds stated below:

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."* , *is not fulfilled.*

The CHMP considered that treatment with sumatriptan needs medical diagnosis and follow-up of the patient, in particular in view of the danger associated with its significant cardiovascular and cerebrovascular adverse effects.

Even if a patient has been initially prescribed sumatriptan following medical diagnosis, patients may undergo changes in cardiovascular and cerebro-vascular risk over time, as a patient's condition changes. Monitoring is also necessary due to possible change in type of headache, possible medication overuse headache and assessment of the need for prophylactic treatment with other medicines.

Therefore, in a non-prescription setting, where sumatriptan would be used without medical supervision and follow-up, this is "*likely to present a danger either directly or indirectly, even if used correctly, if utilised without medical supervision''* as per the first criterion of the guideline.

Cardiovascular and cerebro-vascular adverse events are major safety concerns with sumatriptan use, as triptans have been shown to cause narrowing of coronary arteries and coronary vasospasm. Although previous history of cardiovascular and cerebrovascular disease are contraindicated with sumatriptan, if the non-prescription status be granted under the model proposed by the Applicant, the risks deriving from use by these patients would be greater. This is of particular concern with the use of sumatriptan in patients with a previously unrecognized cardiovascular disease as the cardiovascular status/risks may change over time.

Patient's condition and headache/migraine characteristics, response to treatment, co-medication may change over time, potentially affecting the appropriateness of sumatriptan use. Using sumatriptan, for instance, some migraine patients may suffer from more frequent and more severe attacks. This would require the intervention of a physician to review, modify or suspend sumatriptan use or to initiate prophylactic treatment with other medicines. Detection of misuse, overuse and corrective action would be delayed if patients would not have to consult the doctor anymore.

The CHMP was of the opinion that the addition of contraindications, warnings and information on the use of interacting drugs to the Summary of Product Characteristics and Package Leaflet of Sumatriptan Galpharm as proposed by the Applicant, will not be sufficient to address the concerns related to a non-prescription setting. Patients are unable to evaluate and distinguish between the various contraindications and warnings. Additionally, the CHMP was not convinced that the change in risk for cardiovascular events and migraine status over time could be fully evaluated by patients or pharmacists, thus making sumatriptan unsuitable for the non-prescription setting.

To complement the patient self-assessment, the Applicant proposed a Patient Questionnaire and a Pharmacy Management algorithm as additional risk minimization measures. These did not address the

CHMP concerns and were not considered acceptable as the Patient Questionnaire was long and impractical while the decision tree for the pharmacist was too complex. Additionally, the pharmacist would have been required to take a general medical history. All these aspects were seen as incompatible with the non-prescription principle.

There is wide use and 18 years of clinical experience with sumatriptan as a prescription product, while the non-prescription status is only approved since 2006 in two member states. Thus, the mechanism of action and side-effects of sumatriptan are well-known, whilst the safety profile of non-prescription sumatriptan 50mg (in comparison to the prescription product) has not appropriately been addressed by the Applicant. The data submitted were neither comprehensive nor sufficient. In conclusion, the safety data has not been presented by the Applicant in a way that provided reassurance over the potential dangers associated with the non-prescription status of sumatriptan.

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."

CHMP was of the opinion that medical monitoring is necessary: if patients would not be followed-up by a doctor, there is a potential for wide misuse with the consequence of either medication overuse headache or missing the need for switching to alternative prophylactic treatment. The argumentation made above for the first criterion also supports this.

The CHMP was of the opinion that the first and second criteria for medicinal products subject to medical prescription under Art. 71 of the Directive 2001/83/EC, are met for sumatriptan therefore can not recommend the classification as 'medicinal product not subject to prescription'.

Having considered the above, the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of the above mentioned medicinal product is not properly or sufficiently demonstrated to be authorised as product not subject to prescription.

Therefore, the CHMP recommended the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.

5 Re-examination of the CHMP opinion dated 21 July 2011

Following the CHMP opinion dated 21 July 2011 recommending the refusal of the granting of the marketing Authorisation for Sumatriptan Galpharm, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP on 14 November 2011. The argumentation of the Applicant is summarised in the following five points:

1. The divergent opinion of the Committee;

2. The currently approved non-prescription triptans and the likely approval in the near future of further non-prescription sumatriptan Marketing Authorisations via National Procedures;

3. The extensive published safety data which has been peer reviewed by experts;

4. The results of the user testing of the proposed Package Leaflet in a number of EU Member States in addition to those Member States which already have non-prescription triptans approved.

5. Migraine is a pervasive and debilitating condition which is readily self-diagnosed and treated with OTC analgesics. Convenient and fast access to migraine-specific treatment is important for the quality of life of migraine sufferers.

Additionally, following a request from the applicant as part of their re-examination request, the CHMP convened a Scientific Advisory Group (SAG) consisting of Neurology experts and including General Practitioners, representatives from patient groups and from the Pharmaceutical Group of the European Union (PGEU), representing European Community Pharmacists to provide their views in relation to the marketing authorisation application, taking into account the CHMP grounds for refusal and the applicant's responses to them.

How the above Grounds for re-examination relate to aspects of the original CHMP grounds for refusal, how they were assessed by the CHMP, how the SAG input adds to the picture and aspects covered at the oral explanation to the CHMP on 14 November 2011 is described below.

In reference to the following grounds for refusal in the CHMP original assessment

- The CHMP considered that treatment with sumatriptan needs medical diagnosis and follow-up of the patient in particular in view of its most significant adverse effects (i.e. cardiovascular and cerebrovascular effects).

- CHMP was of the opinion that medical monitoring is necessary: if patients would not be followed-up by a doctor, there is a potential for wide misuse (with the consequence of either medication overuse headache or missing the need for switching to alternative prophylactic treatment).

the Applicant commented as follows:

Risk associated with cardiovascular disease

The applicant referred to several studies mentioned hereinafter.

Reference was made to Welch and Mathew et al. that investigated the cardiovascular safety of sumatriptan using a variety of approaches and study methods. The data from these studies suggest that the chest symptoms sometimes reported after Sumatriptan rarely are linked to ischaemic ECG changes.

The study by Hall and Brown et al including a total of 63,575 migraine patients and 77,239 control subjects was also referred to by the Applicant. This study showed that triptan treatment of migraine does not increase the risk of myocardial infarction cardiovascular death, ischaemic heart disease or mortality.

Velentgas and Cole et al conducted a retrospective study of 130,411 migraineurs (50,383 of whom received a triptan) and 130,411 matched non-migraineurs. This study was performed in response to speculation that the use of triptans or ergot alkaloid drugs might increase risk of ischaemic events through vasoconstriction.
The study showed that there was no increased risk of myocardial infarction with current (adjusted RR 0.80, 95% CI 0.58-1.11) or recent (adjusted RR 1.15, 95% CI 0.71-1.87) triptan use.

Dodick and Lipton et al summarised the evidence reviewed by a panel (composed of an international multidisciplinary group of experts in neurology, primary care, cardiology, pharmacology, women's health and epidemiology) their conclusions about the evidence and their recommendations for the use of triptans in the treatment of migraine. In their conclusion, data obtained from a variety of methodologies including PET, ECG and angiography demonstrate that chest symptoms occurring after use of triptans in some patients are rarely accompanied by evidence of ischaemia. This safety review panel concluded that:

1. Most (but not all) of the triptan safety data are derived from patients without known coronary artery disease.
2. Chest symptoms occurring during use of triptans are generally non-serious and are not explained by ischaemia.
3. The incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears extremely low.
4. The cardiovascular risk-benefit profile of triptans favours their use in absence of contraindications.

The panel concluded that these data show that triptans can be confidently used by migraineurs at low risk of coronary artery disease without the need for prior cardiac status evaluation.

The CHMP noted that the Applicant presented data from the literature focused on the safety profile of sumatriptan. No reassurance relative to the first ground for refusal by CHMP i.e. treatment with sumatriptan needs medical diagnosis and follow-up of the patient, was, however, provided. This CHMP concern has therefore not been addressed by the Applicant. The CHMP considered that the safety profile of sumatriptan is well-known and the cardio-vascular and cerebro-vascular adverse events remained a safety issue for the CHMP.

Patients with cardiac/cerebrovascular conditions treated with sumatriptan could experience an increased risk for adverse events. A trial conducted on 5 patients with variant angina demonstrated coronary artery spasm when sumatriptan was injected intracoronary as opposed to 4 control patients without variant angina (Shimizu et al Intern J Cardiol 2007). This study does not, however, indicate that sumatriptan induce ischemic disorders in healthy subjects.

In addition to the above, there are several publications highlighting safety concerns with the use of triptans in general. A search in PubMed for safety concerns with the use of triptans revealed a number of publications. Notable findings are listed below:

- Although the relatively restricted use of triptans may be attributed to several factors, research suggests that prescribers' concerns about cardiovascular safety prominently figure in limiting their use [Dodick et al, Headache. 2004 May;44 Suppl 1:S20-30].

- Cardiovascular risk-assessment algorithms suggest that patients at low risk (1 or no risk factors) of coronary heart disease can be prescribed triptans without the need for a more intensive cardiovascular evaluation. Conversely, patients with established coronary heart disease or coronary heart disease risk equivalents should not be prescribed triptans according to the current prescribing recommendations. Patients at intermediate risk (2 or more risk factors) of coronary heart disease require cardiovascular evaluation before triptans can be prescribed. Current understanding suggests that the risk of future acute coronary events is a function of the absolute number of vulnerable plaques present, a variable that cannot be accurately determined using available technology or risk-prediction models. Cardiovascular risk-assessment guidelines should be evaluated in the context of this limitation [Papademetriou, Headache. 2004 May;44 Suppl 1:S31-9].

- A recent publication [Barra et al, Expert Opin Pharmacother. 2010 Nov;11(16):2727-37] states that sumatriptan administration can be followed, in close temporal relationship, by Acute Myocardial Infarction in young or adult migraine patients. Some of these cases have developed in subjects taking their first dose. Based on the results of prospective studies, the risk of severe cardiovascular adverse events after the use of a triptan is estimated at 1:100,000 treated attacks. These adverse events,

albeit very infrequent, highlight the importance of careful adherence to the sumatriptan prescribing information.

Diagnosis of migraine can be complex, and it may be difficult for the patient to distinguish migraine from other types of headache. The issue raised by CHMP that treatment with sumatriptan needs medical diagnosis and follow-up of the patient in order to identify those patients with cardiovascular disease, as the cardiovascular status/risks may change over time, remains therefore unresolved.

Risk associated with cerebrovascular disease

The Applicant referred to a study by Hall and Brown et al. which provided epidemiological evidence that there is no association between triptan treatment in migraine and an increased risk of stroke (hazard ratio [HR] 1.13; 95% CI 0.78, 1.65).

It was also pointed out by the Applicant that a retrospective study by Velentgas and Cole et al showed that migraineurs were 67% more likely to suffer a stroke than non-migraineurs (adjusted relative risk [RR] 1.67,95% confidence interval [CI] 1.31-2.13) and that neither current (adjusted RR 0.90, 95% CI 0.64-1.26) nor recent (adjusted RR 0.84, 95% CI 0.46-1.55) triptan use was associated with risk of stroke.

The CHMP considered that the literature data presented by the Applicant had been reviewed previously. The Committee noted a reported case of a 34-year-old woman with no previous migraine history who presented with migraine-like headache, thought to be a first attack of migraine, and who developed brainstem infarction shortly after sumatriptan administration. A detailed etiological evaluation revealed no risk factor for ischemic stroke. The authors believed that the migraine-like headache was the first symptom of cerebral ischemia and that sumatriptan accelerated the development of the infarction [Gazioglu S, Boz C, Ozmenoglu M., Neurol sci. 2011 Jun 17.]

The issue raised by CHMP that treatment with sumatriptan needs medical diagnosis and follow-up of the patient, in order to identify those patients with cerebrovascular disease, as its status/risks may change over time, remains therefore unresolved.

Risk associated with changes in type of headache, medication overuse headache and the need for prophylactic treatment

The Applicant argued that the proposed package leaflet contains all the information necessary for the safe non-prescription use of Sumatriptan Galpharm. This includes clear instructions for migraineurs to visit their physician annually to have their medication reviewed. To this end, previous proposals of questionnaires aiding pharmacists and patients on determining the suitability of sumatriptan treatment were not pursued during the re-examination phase.

The Applicant argued that pack size restriction to 2 tablets only constituted a sufficiently significant barrier to medication overuse.

The CHMP was not convinced that the above points alone would sufficiently address their concerns about changes in type of headache and medication overuse headache.

In addition, the Committee considered that there is a differentiation in the types of headache and a different management strategy for each type (e.g. tensions headache). Such diagnosis and differentiation should be performed by an experienced physician and cannot be left to the subjective judgement of patients.

Patients with frequent migraine attacks are more at risk of medication overuse headache. Migraine attacks sometimes increase in frequency over time. Headache experts conceptualize this process with a model that envisages transition into and out of four distinct states: no migraine, low-frequency episodic migraine (<10 headaches per month), high-frequency episodic migraine (10-14 headaches per month), and chronic migraine (CM, >or=15 headaches per month). Transitions may be in the direction of increasing or decreasing headache frequency and are influenced by specific risk factors. Overall, population studies estimate that patients who have low-frequency episodic migraine or high-frequency episodic migraine will transition to CM at the rate of about 2.5% per year. The influence of medication is modified by both headache attack frequency and frequency of medication use [Goldman MD, Login IS, Headache 2003 Jan;43(1):85-6; author reply 86]

There are also differences in the clinical practice and the diagnosis of migraine. There are several examples of misdiagnosis of migraine in the literature. A case of pituitary haemorrhage was reported [Krimsky W, Weiss H, Headache. 2002 Apr;42(4):291-3]. The patient presented with a sudden bifrontal headache associated with vague transient visual blurring but without nausea or other associated symptoms. After a negative workup at another hospital, including an unremarkable brain computed tomography without contrast, and resolution of headache following treatment with injectable sumatriptan, he was diagnosed with "atypical migraine." The patient's symptoms soon returned, and brain magnetic resonance imaging revealed an enlarged, cystic pituitary gland with a small intraparenchymal haemorrhage.

Clinical approaches to the patient with migraine include step care, whereby all patients begin on a simple or non-specific treatment, stepping up to the next level of therapy if treatment is unsuccessful; or stratified care, whereby first-line therapy is tailored to the severity of the patient's pattern of headache. Studies have demonstrated that for more disabled headache patients, the stratified-care approach results in more robust headache response with less disability and greater cost-effectiveness than step care. Patient satisfaction studies demonstrate that the use of migraine-specific medications (triptans) is associated with a higher satisfaction rate than non-prescription preparations, NSAIDs, and analgesic combinations. Patients who initially reported satisfaction with the latter medications also reported a preference for triptan therapy. Healthcare professionals can assist patients, not only by choosing the most appropriate medication but also by assessing whether the level of benefit the patient is currently receiving could be improved [Diamond M , Cady R, Am J Med. 2005 Mar;118 Suppl 1:18S-27S].

An example of Recurrent occipital seizures misdiagnosed as status migrainosus has been reported [Italiano D, Grugno R, Calabrò RS, Bramanti P, Di Maria F, Ferlazzo E, Epileptic disord 2011 Jun;13(2):197-201]. Peri-ictal headache is commonly reported in patients with epilepsy and often exhibits migraine features. Misdiagnosis is frequent since visual seizures may often be misinterpreted as visual aura of migraine.

For those with high disability levels, migraine-specific acute therapies, such as the triptans, are recommended as the initial treatment, with preventive drugs in selected patients. A variety of behavioural interventions are helpful. Clinicians have in their armamentariums an ever-expanding variety of medications. With experience, clinicians can match individual patient needs with the specific characteristics of a drug to optimize therapeutic benefit [Bigal ME, Lipton RB, Krymchantowski AV, Am J Ther. 2004 Mar-Apr;11(2):130-40].

The existence of guidelines released by the International Headache Society [http://ihs-classification.org/en/02_klassifikation/05_anhang/13.07.01_anhang.html] such as the Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain, is indicative of the need for a step-by-step, careful approach in the diagnosis of migraine and as a consequence the prescription of the appropriate treatment.

The following is a classification of some types of headache

A1. Migraine
A2. Tension-type headache
A3. Cluster headache and other trigeminal autonomic cephalalgias
A6. Headache attributed to cranial or cervical vascular disorder
A7. Headache attributed to non-vascular intracranial disorder
A8. Headache attributed to a substance or its withdrawal
A9. Headache attributed to infection
A10. Headache attributed to disorder of homoeostasis
A11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
A12. Headache attributed to psychiatric disorder
A13. Cranial neuralgias and central causes of facial pain

Therefore, having considered all the above, the CHMP concluded that the issues previously raised about the risk of sumatriptan associated with overuse leading to medication-overuse headache (MOH) and the feasibility of regular disease monitoring and treatment monitoring in a non-prescription setting remained unresolved.

Post Marketing Safety Data

The Applicant argued that the fact that since first becoming available there have not been any major changes to the safety sections of the approved Summary of Product Characteristics constitutes evidence from the Competent Authorities that there are no safety concerns for non-prescription supply.

During the CHMP discussion, the Swedish experience with triptans being available as non prescription was considered. Information concerning the safety of sumatriptan (packages each containing two 50 mg tablets) as reflected in Swedish national databases is provided below:

1. The number of questions concerning sumatriptan to the *National Poison Information Center* at the Karolinska Hospital in Stockholm, Sweden has been fairly constant during the last 10 years. No information about any deaths where sumatriptan could be part of the cause of death has been recorded.

2. The *Swedish National Board of Forensic Medicine* has since the beginning of 2011 the technical abilities to analyze sumatriptan. So far (October 2011) in only one subject undergoing autopsy sumatriptan was found. The subject also had a relatively severe hypokalaemia. No direct association between the death and the sumatriptan concentration could be established.

3. The *Swedish National Board of Health and Welfare* publishes yearly statistics concerning causes of all death related to the whole population of Sweden. In their records for the last 10 years the search term "sumatriptan" has not been found in any single entries in this database. However, the database was designed to regularly supervise only some drugs related to causes of death, e.g. paracetamol. Sumatriptan is not included among these substances.

4. The *Swedish Coronarangio- and Angioplastic Registry* (SCAAR) collects data related to, as the name indicates, coronarangiographic and angioplastic procedures in Sweden. In their records for the last 10 years the search term "sumatriptan" has not been found in any single entries in any of their multiple databases.

5. *The Swedish National Adverse Reactions database* collects information reported to the Swedish MPA by the Swedish Hospitals and primary care providers. No increase in reporting of either headaches and/or cardio vascular events has been reported since the OTC introduction.

In Sweden, where triptans have received non-prescription status and are purchased from shelves in the pharmacies and without mandatory contact with pharmacists, no deaths related to the use of sumatriptan have been recorded in any of the searchable Swedish national health care databases.

As a comparison, non-selective non-aspirin non-steroidal anti-inflammatory drugs [the most common first line drug class for treating migraine] use may account for nearly 34% of all gastrointestinal bleeding cases in the United States, and may have resulted in over 32,000 gastrointestinal bleeding hospitalizations and 3200 gastrointestinal bleeding deaths per year in the 1990s. [Reference: Tarone RE, Blot WJ, McLaughlin JK. Non-selective non-aspirin non-steroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther. 2004 Jan-Feb;11(1):17-25.]

The CHMP acknowledged the above argument that there have not been any significant novel safety signals related to non-prescription supply of sumatriptan. However, this did not reassure the Committee. In general terms, spontaneous report systems may miss some safety signals, especially when the adverse event is a condition prevalent in the general population (e.g. cardiovascular disease). Proactive Post Marketing Surveillance data, e.g. in the form of large scale Phase IV clinical trials and dedicated safety registries would be more appropriate tools to fully characterise the safety profile of a product.

In the view of the CHMP, the absence of additional major spontaneous reports in Member States where sumatriptan is available as non-prescription cannot be considered as a definite proof of lack of safety concerns. Reports in the literature have identified risks with the use of triptans and sumatriptan even in the controlled prescription status (See comments on safety above). Additionally, the CHMP considered that the portion of non-prescription use in the non-prescription setting is relatively small and if there had been an increase in reporting it could have not been detected.

In addition, prescription or over-the-counter NSAIDs with or without oral triptans are commonly used for treatment of acute migraine pain. Little is known about patients' treatment strategy when they have had experiences using NSAIDs and oral triptan co-therapy and the relationship between treatment strategy and migraine symptoms and functionality. Migraine patients frequently change their treatment regimens in response to headache profiles [Ng-Mak DS, Hu XH, Chen YT, Ma L, Headache 2008 Sep;48(8):1176-85].

Revised method of supply and risk minimisation

To take into account differences between EU members states in the supply of non-prescription medicines the Applicant revised their proposals for method of supply to ensure that all the information needed for the migraine sufferer to make the correct informed decision about whether or not to use non-prescription Sumatriptan and how often to visit their physician is present not only at the point of every sale but later when the dose is actually taken. This necessitated developing a leaflet based on the Bulgarian, German, Swedish and UK experience of approved non-prescription triptans and then user testing the resulting proposed leaflet in additional EU members states where OTC triptans are not currently available direct to migraine sufferers. To date successful user testing of the proposed leaflet has taken place in Denmark, Poland, Portugal and Romania. Repeat user testing of the proposed leaflet also took place in Bulgaria where non-prescription Sumatriptan is already available. User testing is also nearing completion in France.

The Applicant argued that in addition to the leaflet, the latest proposed front of pack repeats clear instructions regarding who the medicine is suitable for and consequently who it is not suitable for. As a

consequence the Applicant believed that pharmacy educational material could be cut down to an aide memoire.

The Applicant also argued that the restriction of the pack size to no more than 2 tablets, as well as the products price are measures designed to significantly reduce the likelihood of medication overuse. This strategy has been shown by the German post marketing experience of non-prescription triptans to be effective. This has shown that every individually supplied pack is accompanied by correct and sufficient information to ensure it will be used properly even if a pharmacist is not involved directly in its supply and subsequent consumption. The information is presented as "front of pack" instructions and in the user tested package leaflet, which has meant that the pharmacy information can be reduced to an aide memoire.

The CHMP considered that the information in the front of pack (strap lines) and package leaflet did not provide reassurance of an environment without misuse and/or abuse of the product by migraine sufferers. If misuse has already been reported for migraine medications in the prescription status, it can be expected that cases of misuse will increase in the non-controlled environment of non-prescription status.

In conclusion, the small pack size of 2 tablets could potentially be "by-passed" by a patients during a migraine attack (e.g. visiting more than one pharmacy shops), leading to potential overuse.

In addition to the above-described arguments, the Applicant provided additional information on ad-hoc consultations with the Danish Pharmacy Group and Danish Migraine Patient Association.

The discussion with representatives of the Association of Danish Pharmacies was acknowledged by the CHMP. The Committee in addition also considered the view of Pharmacists' Associations as part of the SAG expertise. It was considered that the view on practice in one MS cannot be representative of all Member States, and it was also noted that there are differences in pharmacy practice across the EU and that in some member states sumatriptan is currently available without prescription, without safety concerns in those countries. The Committee, however, considered that even if it would be possible to harmonise legal supply sub-categories throughout the European Union, specifically to require a 'Pharmacy only' supply, the CHMP would not be sufficiently reassured about the safety concerns in the non-prescription setting in all states across the European Union.

The discussion with the Danish Migraine Patient Association was acknowledged by the CHMP, who also considered the view of Patient Associations as part of the SAG expertise. The above mentioned survey can however be considered as subjective and "pain driven" from migraine sufferers, without having considered the risks associated with the use of sumatriptan in a non-prescription status and under the lack of control and follow-up of a physician.

During the Oral Explanation of 14 November 2011, as further risk minimisation measure, the Applicant expressed their intention to conduct Post-Marketing Studies that in their opinion would generate data specific to non-prescription use. No details on the nature of these studies, their size or their specificity were, however, provided to the CHMP.

Patient Information leaflet – Readability /user testing

In order to ensure that their proposed package leaflet be suitable for non-prescription use Galpharm Ltd performed user testing in a range of EU countries.

The CHMP acknowledged that the applicant had increased the number of Users test. The results of these tests, however, did not convince the CHMP that the information provided in the package leaflet

and in the front of the pack constituted sufficient reassurance that the issues of misuse and/or abuse of the product by migraine sufferers would be addressed.

The CHMP was of the opinion that the addition of contraindications, warnings and information on the use of interacting drugs to the Summary of Product Characteristics and Package Leaflet of Sumatriptan Galpharm as proposed by the Applicant will not be sufficient to address the concerns related to a non-prescription setting. Patients are unable to evaluate and distinguish between the various contraindications and warnings. Additionally, the CHMP was not convinced that the change in risk for cardiovascular events and migraine status over time could be fully evaluated by patients, thus making sumatriptan unsuitable for the non-prescription setting.

Access to currently approved non-prescription triptans in Europe

The Applicant pointed out that non-prerscription triptans have been approved in Europe via National Procedures. Since 2006, a number of non-prescription triptan Marketing Authorisations, including sumatriptan, have been granted within the European Union. The Applicant stated that there are currently several non-prescription triptan Marketing Authorisations approved within the European Union, in Germany, Bulgaria, Sweden and the United Kingdom.

The Applicant's argument that non-prescription status for triptans has already been approved within the EU was noted by the CHMP. However, the limited information on the use of sumatriptan in a small number of Member States was not considered sufficient to extrapolate and grant a Marketing Authorisation for the whole of the EU. With regards to the argument that if a product is considered safe for non-prescription use in one Member State this would necessarily extend to other European Member States, the CHMP considered that the following potential concerns were to be addressed, not linked to the intrinsic properties of the molecule per se:

a) the complexity of the condition in relation to the accuracy of the diagnosis and the identified safety concerns;

b) the differences in the national health systems;

c) the diversity in clinical and pharmacy practices;

d) in the context of self-assessment, the subjective "performance" of the migraine sufferer, given the variability in level of culture, tradition and education across Europe.

In addition to the above, the CHMP was concerned that self medication is not appropriate in this particular health condition, as migraine patients would potentially have delayed access to their respective Healthcare Systems with potentially detrimental effects on their health if Sumatriptan would be given a non-prescription status.

Report from the SAG

A Scientific Advisory Group in Neurology (with additional experts from patient groups and from the Pharmaceutical Group of the European Union - PGEU, representing European Community Pharmacists) convened on 27 October 2011 in the context of the re-examination procedure for Sumatriptan Galpharm, to provide advice on a specific list of questions adopted by the CHMP at its October 2011 meeting.

In this context, the Rapporteur and Co-Rapporteur provided the SAG with an overview of the issues to be discussed and summarised the questions to the SAG. A presentation by the Applicant followed. The

meeting ended with a summary of the discussion, and the agreement of an answer for each of the issues. The applicant was briefed about the conclusions that the SAG would communicate to the CHMP. The CHMP questions and the answers provided by the SAG as an outcome are presented below.

1. **The Rapporteurs have assessed the Applicants response to the grounds for refusal in the initial opinion from CHMP. The SAG is asked to comment on the grounds for refusal and the assessments.**

   SAG response: This question is largely covered by the responses to questions 2-5 below. Regarding the cardiovascular and cerebrovascular safety for sumatriptan, see response to question 5. For the impact of legal status on the risk for sumatriptan overuse, see response to question 4. Regarding the assessment of the need for prophylactic treatment with other medicinal products, the SAG considered that if a patient has more than 3 migraine attacks per month, the pharmacist should refer the patient to a physician for investigation and for assessment of the need for prophylactic treatment.

2. **The SAG is invited to discuss the pros and cons of sumatriptan in the proposed non-prescription setting taking into account the proposed indication for patients earlier diagnosed with migraine (i.e. 'Sumatriptan Galpharm should only be used where there is a clear diagnosis of migraine'), and the package size of two tablets.**

   SAG response:
   The pros of sumatriptan in the non-prescription setting would be:
   -Ease of access to a drug of proven efficacy;
   -Useful in case of a "rescue situation" (e.g. when patients run out of their prescription supply, or they go away for a short time forgetting their medication);
   -No clear signal for an increased risk for cardiovascular or cerebrovascular adverse events in the adult population (between 18 and 65 years old).

   The cons would be:
   -Diagnosis of migraine can be complex, and it may be difficult for the patient and pharmacist to distinguish migraine from other types of headache;
   -There are insufficient data with regard to the risk of overuse in the non-prescription setting;
   -The cardiovascular risk in patients treated long-term may change over time;
   -Patients with frequent migraine attacks are more at risk of medication overuse headache. If a patient has more than 3 migraine attacks per month, the pharmacist should refer the patient to a physician for investigation and for consideration of prophylactic treatment.
   -The SAG recommended that non-prescription sumatriptan should only be dispensed under supervision of pharmacists. The SAG was concerned that the risk of misuse or abuse of sumatriptan can increase if there is no control by a pharmacist when dispensing sumatriptan, and when sumatriptan is available outside of pharmacies. This will be the case in some member states, where sales of non-prescription drugs can not be restricted to pharmacy only category. The same concern applies to the possibility that sumatriptan may be sold via internet.

3. **The SAG is asked to comment on the following issues:**

   - **Differences in efficacy and safety of treatment options of migraine e.g. NSAID or e.g. sumatriptan when taken in suggested non-prescription doses.**

   SAG response: The SAG considered that there were no clear differences in efficacy between NSAIDs and oral sumatriptan when taken in suggested non-prescription doses. Regarding safety, for occasional migraine attacks each type of treatment has its own safety implications, but it cannot be concluded that one drug has a worse safety profile than another. If used for frequent migraine attacks, both NSAIDs and sumatriptan can give medication overuse headache (although the risk seems to be higher for the triptan class), and for NSAIDs, there is an increased risk for gastrointestinal bleeding.

- **Potential medical consequences/risks if sumatriptan 50 mg in pack size of two tablets are sold non-prescription in pharmacies. How likely is it and what evidence exists that a subpopulation of migraine patients would turn into long term self medication?**

SAG response: There are at present insufficient data regarding this issue. It is known that approximately 10-12 % of patients will overuse sumatriptan in the prescription-only setting. Identified risks factors for this subpopulation are a high frequency of migraine (above 10 or 12 per month) and/or psychological profile of drug abuser. However, from the available data it can not be concluded if this subpopulation of patients will increase in a non-prescription setting.

4. **How does the SAG assess the impact of the legal status (prescription only or non-prescription) on the risk for sumatriptan overuse (for any type of headache)?**

SAG response: In countries where sumatriptan is used as non-prescription, there are no signs that the risk for overuse of sumatriptan has increased, and the small pack-size and increased cost vs. the prescription-only medicine will not be an incentive for some patients. However, more data is needed on this topic.

5. **SAG is requested to comment on the cerebrovascular and cardiovascular safety of sumatriptan and the potential impact of the legal status (prescription only or non-prescription) on these specific aspects and on the safe use of sumatriptan in general.**

SAG response: It is known from the literature that there is an increased risk for cardio- and cerebrovascular disease in patients with migraine, particularly those with aura, regardless of whether they are taking triptans or not. The SAG considered that there is no significant signal of an increased risk for cardiovascular or cerebrovascular adverse events with sumatriptan use in the adult population between 18 and 65 years old, and the SAG did not see any specific concerns with regard to the legal status for sumatriptan in this age group. There are weak data suggesting that cardiovascular and cerebrovascular adverse events may not increase in triptan abusers. However there may be an under notification in this group. The risk for cerebrovascular and cardiovascular side effects increases with age. In the elderly above 65 years, there is at present insufficient safety data, and it was noted that sumatriptan is not indicated in this patient group.

6 Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant in writing and in an oral explanation on 14 November 2011, taking into account the views of the Scientific Advisory Group.

The Committee noted that the Applicant's arguments were similar to previously assessed proposals. The CHMP considered that the issues concerning the risk associated with potential cardiovascular and cerebrovascular adverse effects of sumatriptan as well as the potential for misuse with the consequence of either medication overuse headache (MOH) or missing the need for switching to alternative prophylactic treatment remained unresolved.

The CHMP noted the SAG's position, especially with regards to the extent of the possible cardiovascular risk. The Committee, however, reiterated that, due to contraindications and the adverse event profile of the product (e.g. cardio/cerebrovascular effects) some primary and secondary care guidelines concerning migraine place triptans as second line in their treatment recommendations.

The CHMP was furthermore still of the view that treatment with sumatriptan requires a medical diagnosis of migraine and follow-up of the patient headache.

The Applicant did not comment explicitly on the risk of medication overuse headache (MOH) related to triptans as this issue was raised by the CHMP as an argument not to recommend the approval of Sumatriptan Galpharm with non-prescription status.

The CHMP considered that Sumatriptan is indeed a useful medication for the management of migraine but concerns remained over its safety in a non-prescription setting. The switch to a non-prescription status would create a direct risk of misdiagnosing migraine and indirect risk with misuse, abuse and interactions with concomitant medications. Changing the classification of Sumatriptan to non-prescription, even following a previous medical diagnosis, could also result in:

- delay or absence of assessment of coronary artery disease;
- inappropriate treatment of mixed headaches/migraine;
- delay in the detection of overuse with the risk of the development of triptan overuse headache (MOH);
- delay in assessment of the need for migraine prophylaxis.

The CHMP was of the opinion that the proposed risk minimisation activities (including the limitation of the pack-size to two tablets and the recommendation to consult the doctor regularly) were not able to reduce the risks to an acceptable level.

Based on the above, the first and second criteria for medical prescription under Article 71 of the Directive 2001/83, remain not fulfilled and therefore it is not recommended to change the classification of sumatriptan from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription".

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Sumatriptan Galpharm in the applied indication was unfavourable and that the application did not satisfy the criteria for authorisation. The CHMP recommended the refusal of the granting of the marketing authorisation.

The grounds for the decision are as follows:

Based on their review of the data on safety and efficacy, and in line with the provisions of Art. 71 of Directive 2001/83/EC and the EC 'Guideline on Changing the Classification for the Supply of a Medicinal product for Human Use' (The Rules governing Medicinal Products in the European Community, Volume 2C: Guidelines), the CHMP considered that the safety of Sumatriptan Galpharm for the "acute relief of migraine attacks, with or without aura" has not been sufficiently demonstrated for the non-prescription status as detailed in the grounds stated below:

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." , is not fulfilled.*

The CHMP considered that treatment with sumatriptan needs medical diagnosis and follow-up of the patient, in particular in view of the danger associated with its significant cardiovascular and cerebrovascular adverse effects.

Even if a patient has been initially prescribed sumatriptan following medical diagnosis, patients may undergo changes in cardiovascular and cerebro-vascular risk over time, as a patient's condition changes. Monitoring is also necessary due to possible change in type of headache, possible medication overuse headache and assessment of the need for prophylactic treatment with other medicines.

Therefore, in a non-prescription setting, where sumatriptan would be used without medical supervision and follow-up, this is "*likely to present a danger either directly or indirectly, even if used correctly, if utilised without medical supervision''* as per the first criterion of the guideline.

Cardiovascular and cerebro-vascular adverse events are major safety concerns with sumatriptan use, as triptans have been shown to cause narrowing of coronary arteries and coronary vasospasm. Although previous history of cardiovascular and cerebrovascular disease are contraindicated with sumatriptan, if the non-prescription status be granted under the model proposed by the Applicant, the risks deriving from use by these patients would be greater. This is of particular concern with the use of sumatriptan in patients with a previously unrecognized cardiovascular disease as the cardiovascular status/risks may change over time.

Patient's condition and headache/migraine characteristics, response to treatment, co-medication may change over time, potentially affecting the appropriateness of sumatriptan use. Using sumatriptan, for instance, some migraine patients may suffer from more frequent and more severe attacks. This would require the intervention of a physician to review, modify or suspend sumatriptan use or to initiate prophylactic treatment with other medicines. Detection of misuse, overuse and corrective action would be delayed if patients would not have to consult the doctor anymore.

The CHMP was of the opinion that the addition of contraindications, warnings and information on the use of interacting drugs to the Summary of Product Characteristics and Package Leaflet of Sumatriptan Galpharm as proposed by the Applicant, will not be sufficient to address the concerns related to a non-prescription setting. Patients are unable to evaluate and distinguish between the various contraindications and warnings. Additionally, the CHMP was not convinced that the change in risk for cardiovascular events and migraine status over time could be fully evaluated by patients, thus making sumatriptan unsuitable for the non-prescription setting.

There is wide use and 18 years of clinical experience with sumatriptan as a prescription product, while the non-prescription status is only approved since 2006 in a limited number of member states. Thus, the mechanism of action and side-effects of sumatriptan are well-known, whilst the safety profile of non-prescription sumatriptan 50mg (in comparison to the prescription product) has not appropriately been addressed by the Applicant. The data submitted were neither comprehensive nor sufficient. In conclusion, the safety data has not been presented by the Applicant in a way that provided reassurance over the potential dangers associated with the non-prescription status of sumatriptan.

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."

CHMP was of the opinion that medical monitoring is necessary: if patients would not be followed-up by a doctor, there is a potential for wide misuse with the consequence of either medication overuse headache or missing the need for switching to alternative prophylactic treatment. The argumentation made above for the first criterion also supports this.

The CHMP was of the opinion that the first and second criteria for medicinal products subject to medical prescription under Art. 71 of the Directive 2001/83/EC, are met for sumatriptan therefore can not recommend the classification as 'medicinal product not subject to prescription'.

Having considered the above, the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of the above mentioned medicinal product is not properly or sufficiently demonstrated to be authorised as product not subject to prescription.

Therefore, the CHMP recommended the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.

Divergent positions to the majority recommendation are appended below.

7 Appendix

DIVERGENT POSITIONS

The following members of CHMP did not agree with the CHMP's Opinion on the Re-examination of the marketing authorisation application for *Sumatriptan Galpharm 50mg* (EMA/H/C/002140) taken on 14 November 2011, for the following reasons:

Sumatriptan is an effective treatment for migraine symptoms and has been widely used as a non-prescription medicine for a number of years in several member states, without additional safety concerns arising. More than 30% of the total population of the European Union currently has access to non-prescription triptans for the treatment of migraine. There is clear scientific justification, underpinned by a substantial evidence base, for concluding that a positive benefit/risk profile has been established for non-prescription sumatriptan. There is no evidence to suggest non-prescription availability presents a danger, either directly or indirectly, nor that existing non-prescription products are frequently used incorrectly.

Migraine is a well established non-prescription condition
Many existing non-prescription medicines are licensed, throughout the EU, for use in the treatment of migraine: there is no evidence that the availability of these medicines interferes with patients seeking medical advice in relation to prophylaxis of migraine. Patients and pharmacists are used to managing migraine in the non-prescription setting, with no evidence of a significant risk of inappropriate treatment.

Migraineurs are sufficiently knowledgeable about their condition to realise when their symptoms are changing. The patient information leaflet includes clear advice to talk to your doctor if symptoms have changed.

Non-prescription supply is not associated with an increased risk of cardiovascular or cerebrovascular side effects
There is no evidence of any difference in the risk of adverse events with non-prescription use compared with POM sumatriptan, as shown by reference to both registry data and spontaneous reports. The Scientific Advisory Group (SAG) considered that there is no significant risk of cardiovascular and cerebrovascular adverse events in the adult population between 18 and 65 years old and the SAG did not have any specific concerns with regard to non-prescription availability for Sumatriptan in this age group on safety grounds.

Many OTC medicines are contraindicated for patients with conditions which may develop over time (for example, aspirin and kidney disease). Detailed patient information would enable safe and effective use of sumatriptan in the non-prescription setting by highlighting the key warnings and contra-indications, and the importance of seeking advice from a healthcare professional when appropriate.

Non-prescription supply is not associated with an increased risk of inappropriate use leading to medication overuse headache (MOH)
There are no signs that the risk of overuse of sumatriptan is increased in countries where sumatriptan is available without prescription, and this was noted by the SAG. No recent scientific data show an increased risk of MOH when migraine is managed with triptans compared with other medication such as analgesics. Small pack size (two tablets) and relevant patient information are effective measures to manage the risk of MOH. Patients are very aware of their condition and would notice any change in their symptom profile: there are no increased safety concerns associated with sumatriptan in relation to inappropriate self-treatment.

Measures to ensure safe use in the non-prescription setting
The proposed carton label and patient information leaflet provide clear information about who can use the product, when not to use it, how to use it, and when to seek advice from a doctor or pharmacist if in doubt.

Further risk minimisation was provided by *Sumatriptan Galpharm 50mg* being proposed for use only by patients who have already been diagnosed with migraine and previously treated with Sumatriptan.

Significant public health benefits for migraine sufferers
As sumatriptan is most effective if taken at onset of an attack, rapid access to 2 tablet pack, without the need to seek a prescription, there is a clear benefit to enabling sufferers to treat and manage their condition effectively without unnecessary delay.

The following CHMP Members therefore consider that the benefit/risk ratio of sumatriptan with non-prescription legal status is positive and would justify the granting of a marketing authorisation for *Sumatriptan Galpharm 50mg*.

London, 17 November 2011

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