Public Assessment Report

Decentralised Procedure

Aripiprazole 1mg/ml Oral Solution

(aripiprazole)

Procedure No: UK/H/5795/001/DC

UK Licence No: PL 24668/0264

Caduceus Pharma Limited
LAY SUMMARY

Aripiprazole 1mg/ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Aripiprazole 1mg/ml Oral Solution (PL 24668/0264; UK/H/5795/001/DC). It explains how the application for Aripiprazole 1mg/ml Oral Solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Aripiprazole 1mg/ml Oral Solution. For practical information about using Aripiprazole 1mg/ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Aripiprazole Oral Solution’ in this report.

What is Aripiprazole Oral Solution and what is it used for?
Aripiprazole Oral Solution is a ‘generic medicine’. This means that Aripiprazole Oral Solution is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK).

Aripiprazole Oral Solution is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Aripiprazole Oral Solution is also used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults, it also prevents this condition from returning in patients who have responded to the treatment with Aripiprazole Oral Solution.

How does Aripiprazole Oral Solution work?
Aripiprazole Oral Solution contains the active substance, aripiprazole, which belongs to a group of medicines called antipsychotics. These medicines work by affecting the activity of some key brain chemicals.

How is Aripiprazole Oral Solution used?
Aripiprazole Oral Solution is for oral use (taken by mouth). The patient should always take this medicine exactly as the doctor or pharmacist has advised. If unsure, the patient should ask the doctor or pharmacist.

The recommended dose for adults is 15 ml solution (corresponding to 15 mg aripiprazole) once a day. However the patient’s doctor may prescribe a lower or higher dose to a maximum of 30 mg (i.e. 30 ml) once a day.

Use in children and adolescents
Aripiprazole Oral Solution may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the recommended dose for adolescents of 10 mg once a day. However the patient’s doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Measuring the dose
- Doses up to 5 ml should be measured using the 5 ml syringe supplied in the carton.
- Doses of 10 ml and more should be measured using the measuring cup or the 5 ml syringe supplied in the carton.
Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

This medicine can only be obtained with a prescription.

**What benefits of Aripiprazole Oral Solution have been shown in studies?**

As Aripiprazole Oral Solution is a generic medicine, studies in patients have been limited to tests to determine that Aripiprazole Oral Solution is bioequivalent to the reference medicine Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Aripiprazole Oral Solution?**

Like all medicines, Aripiprazole Oral Solution can cause side effects although not everybody gets them.

For the full list of all side effects reported with Aripiprazole Oral Solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Aripiprazole Oral Solution.

**Why Aripiprazole Oral Solution approved?**

It was concluded that, in accordance with EU requirements, Aripiprazole Oral Solution has been shown to have comparable quality and to be bioequivalent to Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK).

Therefore, the MHRA decided that, as for Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK), the benefits outweigh the identified risks and recommended that Aripiprazole Oral Solution can be approved for use.

**What measures are being taken to ensure the safe and effective use of Aripiprazole Oral Solution?**

A Risk Management Plan has been developed to ensure that Aripiprazole Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Aripiprazole Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Aripiprazole Oral Solution.

Iceland and the UK agreed on 17 February 2016 to grant a Marketing Authorisation for Aripiprazole Oral Solution. A Marketing Authorisation was granted in the UK to Caduceus Pharma Limited on 22 February 2016.

The full PAR for Aripiprazole Oral Solution follows this summary.

For more information about treatment with Aripiprazole Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2016.
SCIENTIFIC DISCUSSION

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Scientific discussion

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Aripiprazole 1mg/ml Oral solution (PL 24668/0264; UK/H/5795/001/DC) could be approved. The product may be referred to as ‘Aripiprazole Oral Solution’ in this report.

Aripiprazole Oral Solution is a Prescription Only Medicine (POM), which is indicated for the treatment:
- of schizophrenia in adults and in adolescents aged 15 years and older
- of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment
- up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application cross-referring to the reference product Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK), which was authorised via the Centralised Procedure on 04 June 2004.

Aripiprazole exhibits high affinity for dopamine D2 and D3, serotonin 5HT₁A and 5HT₂A receptors, moderate affinity for dopamine D₄, serotonin 5HT₂C and 5HT₇, α₁-adrenergic and histamine H₁ receptors, and moderate affinity for the serotonin reuptake site. Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors. Aripiprazole functions as a partial agonist at the dopamine D₂ and the serotonin 5HT₁A receptors, and as an antagonist at serotonin 5HT₂A receptor.

The precise mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through the combination of partial agonist activity at D₂ and 5HT₁A receptors and antagonist activity at 5HT₂A receptors. Actions at receptors other than D₂, 5HT₁A, and 5HT₂A may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic α₁ receptors.

Two bioequivalence studies (one parallel study and one cross-over study) were submitted to support this application comparing the applicant’s test product Aripiprazole 1mg/ml oral solution with the reference product Abilify (aripiprazole) 1mg/ml oral solution (Otsuka Pharmaceutical Europe Limited, UK) under fasting conditions. The applicant has stated that the bioequivalence studies were conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements and the Declaration of Helsinki.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 228) on 17 February 2016. After a subsequent national phase, a licence was granted in the UK on 22 February 2016.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Aripiprazole Oral solution is available as a clear colourless liquid. Each millilitre (ml) of oral solution contains 1 milligram (mg) aripiprazole, as the active substance. The product also contains pharmaceutical excipients namely, propylene glycol (E1520), macrogol 4000, phosphoric acid, hypromellose 2910, erythritol (E 968), sucralose (E 955), sodium benzoate (E211), disodium edetate, N&A Flavour for grape 26436 (which contains flavouring ingredients and propylene glycol (E1520)) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in:
1 amber coloured polyethylene terephthalate (PET) bottles each closed with a white plastic (high density polyethylene/polypropylene [HDPE/PP]), child-resistant, screw cap with a white polyethylene syringe adaptor. Each carton contains one bottle, an oral syringe and a measuring cup. The syringe body is made of PP and the plunger is made of HDPE and is graduated for dosing of 0.5 ml and then every 0.5 ml up to 5 ml. The measuring cup is PP and is graduated for dosing of 5 ml, 10 ml, 15 ml, 20 ml, 25 ml and a maximum volume of 30 ml.
2 amber coloured glass bottles each closed with a white plastic (HDPE/PP), child-resistant, screw cap with a white polyethylene syringe adaptor. Each carton contains one bottle, an oral syringe and a measuring cup. The syringe body is made of PP and the plunger is made of HDPE and is graduated for dosing of 0.5 ml and then every 0.5 ml up to 5 ml. The measuring cup is PP and is graduated for dosing of 5 ml, 10 ml, 15 ml, 20 ml, 25 ml and a maximum volume of 30 ml.

The product is available in a pack size of 150 ml.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Aripiprazole
INN: Aripiprazole
Chemical names: 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4- dihydroquinolin-2-(1H)-one

Structural formula:

\[
\begin{align*}
\text{Molecular formula:} & \quad C_{23}H_{27}Cl_2N_3O_2 \\
\text{Molecular mass:} & \quad 448.4 \text{ g/mol} \\
\text{Appearance:} & \quad \text{White or almost white crystals or crystalline powder} \\
\text{Solubility:} & \quad \text{Practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol (96%).}
\end{align*}
\]

Aripiprazole is the subject of a European Pharmacopoeia monograph.
Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**II.3 MEDICINAL PRODUCT**

**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to produce an oral solution containing 1mg/ml of aripiprazole that could be considered a generic medicinal product of the innovator product Abilify 1 mg/ml Oral Solution (Otsuka Pharmaceutical Europe Limited, UK). Suitable pharmaceutical development data have been provided for this application.

With the exception of N&A (natural and artificial) Flavour for grape 26436 (and its constituent flavourings), all the excipients comply with their respective European Pharmacopoeia monographs. N&A Flavour for grape 26436 is controlled to a suitable in-house specification. In addition, N&A Flavour for grape 26436 complies with the requirements of EC Regulation No. 1334/2008 as amended, on flavourings and certain food ingredients with flavouring properties for use in and on foods.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

**Control of Finished Product**

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the unopened product and 6 months after first opening the product, with the special storage conditions ‘Store in the original bottle in order to protect from light.’ has been accepted. This medicinal product does not require any special temperature storage conditions.
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section IV, Clinical Aspects.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

It is recommended that a Marketing Authorisation is granted for Aripiprazole 1 mg/ml Oral Solution.

**II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

![Aripiprazole Oral Solution Label](image)
III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known. As aripiprazole is a widely used, well-known active substance, the applicant has not provided new non-clinical data for this application and none are required. An overview based on literature review is, thus, appropriate.
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### III.2 Pharmacology
No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

### III.3 Pharmacokinetics
No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

### III.4 Toxicology
No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

### III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, the risks to the environment are not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

### III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

It is recommended that a Marketing Authorisation is granted for Aripiprazole 1mg/ml Oral Solution, from a non-clinical point of view.

### IV. CLINICAL ASPECTS

#### IV.1 Introduction
The clinical pharmacology of aripiprazole is well-known.

Initially, no bioequivalence studies were submitted to support this application; a biowaiver was sought on the basis that the proposed product and the reference product are oral aqueous solution at the time of administration. According to the regulatory requirements, the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study is required for oral aqueous solutions if the excipients may affect the gastrointestinal transit, in vivo solubility or in vivo stability of the active substance, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. As the proposed product contains an excipient (macrogol 4000) that may affect gastrointestinal transit and this excipient is absent in the reference product, in response to an objection raised concerning the justification for a biowaiver, the applicant submitted two bioequivalence studies to support the application.

Initially, due to the long half-life of aripiprazole, a parallel study instead of a conventional crossover study was performed in order to conduct the study as quickly as possible. However, the parallel study failed on the AUC₀₋₇₂ parameter and consequently a crossover study was conducted to perform the comparison of the test and reference products within the same subjects.

The results of the cross-over study demonstrated bioequivalence between test and reference products.
With the exception of data from the bioequivalence studies detailed below, no new clinical data are provided or are required for this application.

**IV.2 Pharmacokinetics**

In support of this application, the applicant submitted the following bioequivalence studies.

**Study 1**

An open label, randomised, single dose, parallel bioequivalence study to compare the bioavailability of the applicant’s test product, Aripiprazole 1mg/ml solution (Balkan pharma) versus that of the reference product, Abilify 1mg/ml oral solution (Otsuka Pharmaceutical Europe Limited, UK) in healthy adult subjects under fasting conditions.

The subjects were administered a single oral dose of the test or reference product on one occasion with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected for plasma levels before and up to and including 72 hours after each administration. The pharmacokinetic results of the study are presented in the following table:

| Table 1. Ratio and 90% Confidence Intervals of Test Product versus Reference Product |
|---------------------------------|----------------------|----------------------|
| Ratio (Test/Reference) - %      | AUC_{0-72}           | C_{max}              |
| 86.86                           | 89.55                |

- \( C_{\text{max}} \): maximum plasma concentration over the time span specified
- \( \text{AUC}_{0-72} \): area under the plasma concentration-time curve from time zero to 72 hours
- CV%: percentage coefficient of variation
- Ratios and 90% CI calculated from ln-transformed data

According to the results of the safety analysis, there were no serious adverse events (AEs) in the study and both the test and reference product were found to be well tolerated.

**Conclusion of Study 1**

Both the test and reference product were found to be well tolerated. However, the 90% confidence intervals of the test/reference ratio for \( \text{AUC}_{0-72} \) and \( C_{\text{max}} \) values do not lie within the acceptable limits of 80.00 % to 125.00%, in line with Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Hence, the applicant’s test product has not been shown to be bioequivalent to the reference product Abilify (aripiprazole) 1mg/ml oral solution (Otsuka Pharmaceutical Europe Limited, UK) under fasting conditions. Therefore, the applicant additionally submitted the second study below to support the application.

**Study 2**

An open label, randomised, single dose, two way, crossover bioequivalence study comparing the bioavailability of the applicant’s test product Aripiprazole 1mg/ml solution versus that of the reference product Abilify (aripiprazole) 1mg/ml oral solution Otsuka Pharmaceutical Europe Limited, UK), in healthy human, adult subjects under fasting conditions.

The subjects were administered a single oral dose (1 × 10 ml of solution) of either the test or reference product. Blood samples were collected for plasma levels before and up to and including 72 hours after each administration. The washout period between the treatment phases was 35 days. The pharmacokinetic results of the study are presented in the following tables:
Table 2 – Summary of pharmacokinetic data for aripiprazole

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-72} (Reference Product)</td>
<td>2418.60</td>
<td>2447.70</td>
<td>388.748</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>69.01</td>
<td>70.22</td>
<td>13.909</td>
</tr>
<tr>
<td>AUC_{0-72} (Test product)</td>
<td>2295.53</td>
<td>2324.52</td>
<td>377.314</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>64.17</td>
<td>64.93</td>
<td>9.776</td>
</tr>
</tbody>
</table>

C_{max} maximum plasma concentration over the time span specified
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours

Table 3 – Ratio and 90% Confidence Intervals of Test Product versus Reference Product

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Ratio (%)</th>
<th>90% Intervals</th>
<th>Confidence</th>
<th>Intra Subject Variability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-72}</td>
<td>94.91</td>
<td>91.19</td>
<td>98.79</td>
<td>8.09</td>
</tr>
<tr>
<td>C_{max}</td>
<td>92.98</td>
<td>86.33</td>
<td>100.14</td>
<td>15.05</td>
</tr>
</tbody>
</table>

C_{max} maximum plasma concentration over the time span specified
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
Ratios and 90% CI calculated from ln-transformed data

According to the results of the safety analysis, there were no serious AEs in the study and both the test and reference product were found to be well tolerated.

Conclusion of Study 2
The 90% confidence intervals of the test/reference ratio for AUC_{0-72} and C_{max} values lie within the acceptable limits of 80.00 % to 125.00%, in line with Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Hence, the applicant’s test product has been shown to be bioequivalent to the reference product Abilify (aripiprazole) 1mg/ml oral solution (Otsuka Pharmaceutical Europe Limited, UK) under fasting conditions. Both the test and reference product were found to be well tolerated.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of aripiprazole are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of aripiprazole is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
The safety profile of aripiprazole is well-known. With the exception of the safety data generated during the bioequivalence studies no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence studies.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aripiprazole 1mg/ml Oral solution.

A summary of safety concerns is listed in the table below:
Summary of safety concerns

| Important identified risks | Extrapyramidal symptoms, including tardive dyskinesia  
Neuroleptic Malignant Syndrome |
|---------------------------|--------------------------------------------------|
| Important potential risks | Suicide related events  
Seizure  
Hyperglycaemia and diabetes mellitus  
Orthostatic hypotension  
Dyslipidemia |
| Missing information       | Safety in pregnancy and lactation  
Safety in paediatrics |

Routine pharmacovigilance is proposed for all safety concerns.

Routine risk minimisation is proposed for all safety concerns with the exception of ‘extrapyramidal symptoms, including tardive dyskinesia’ and ‘safety in paediatrics’ For these, an information pack containing the SmPC, PIL, educational materials for patients and care givers and educational materials for healthcare professionals is proposed. This is consistent with the additional risk minimisation measures of the reference product for the indication “treatment of up to 12 weeks of moderate to severe manic episodes in Bipolar I disorder in adolescents aged 13 years and older”.

In each Member State where the indication of Aripiprazole Caduceus for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where the indication of Aripiprazole Caduceus for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older, the following are made available:

1. Educational material for healthcare professionals
2. Educational material for the patients and their caregivers

Key elements of the Healthcare Professional FAQ Brochure (Q&A form) intended for Healthcare Providers treating adolescent patients with bipolar mania:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Instructions reinforcing that the intended age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age due to safety concerns
- Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
- Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
- Reminder to educate patients/caregivers and provide the Patient/Caregiver Information Brochure

Key elements of the Patients/Caregiver Information Brochure:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Information that the indicated age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age
• Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
• Request to inform the physician of all medical conditions before treatment
• The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Aripiprazole 1mg/ml Oral Solution.

V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Aripiprazole 1mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of aripiprazole are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s test product and the reference product Abilify (aripiprazole) 1mg/ml oral solution (Otsuka Pharmaceutical Europe Limited, UK), under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of aripiprazole is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

The safety profile of aripiprazole is well-known. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.
**PRODUCT LITERATURE**
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

**BENEFIT/RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with aripiprazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

**RECOMMENDATION**
The grant of a Marketing Authorisation is recommended.
## Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>