



Australian Government

Department of Health

Therapeutic Goods Administration

# Australian Public Assessment Report for Aripiprazole Monohydrate

Proprietary Product Name: Abilify Maintena

Sponsor: Lundbeck (Australia) Pty Ltd

**November 2014**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

### Copyright

© Commonwealth of Australia 2014

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

<b>List of common abbreviations used in this AusPAR</b>	<b>5</b>
<b>I. Introduction to product submission</b>	<b>6</b>
Submission details	6
Product background	6
Regulatory status	7
Product Information	8
<b>II. Quality findings</b>	<b>8</b>
Drug substance (active ingredient)	8
Drug product	8
Evaluation of sterility aspects	8
Biopharmaceutics	9
Quality summary and conclusions	9
<b>III. Nonclinical findings</b>	<b>10</b>
Introduction	10
Pharmacology	10
Pharmacokinetics	10
Toxicology	11
Nonclinical summary and conclusions	16
Nonclinical conclusions and recommendation	17
<b>IV. Clinical findings</b>	<b>18</b>
Introduction	18
Pharmacokinetics	20
Pharmacodynamics	23
Dosage selection for the pivotal studies	23
Efficacy	23
Safety	26
First round benefit-risk assessment	30
First round recommendation regarding authorisation	31
Clinical questions	32
Second round benefit-risk assessment	32
Second round recommendation regarding authorisation	32
<b>V. Pharmacovigilance findings</b>	<b>32</b>
Risk management plan	32
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>41</b>
Quality	41

Nonclinical _____	41
Clinical _____	42
Risk management plan _____	42
Risk-benefit analysis _____	42
Outcome _____	50
<b>Attachment 1. Product Information _____</b>	<b>51</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report _____</b>	<b>51</b>

## List of common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
AUC	Area under concentration versus time curve
CI	Confidence interval
C <sub>max</sub>	Peak (or maximum) concentration
EU	European Union
EMA	European Medicines Agency
GCP	Good Clinical Practice
IM	Intramuscular
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamic
PK	Pharmacokinetic
PSP	Personal and Social Performance Scale
SAE	Serious adverse event

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	Major variation (New strength and new dosage form)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	22 July 2014
<i>Active ingredient:</i>	Aripiprazole Monohydrate
<i>Product name:</i>	Abilify Maintena
<i>Sponsor's name and address:</i>	Lundbeck (Australia) Pty Ltd 1 Innovation Rd North Ryde NSW 2113
<i>Dose forms:</i>	Lyophilised powder and solvent for reconstitution
<i>Strengths:</i>	Dosage strength when reconstituted (in 2 mL water) is 300 mg or 400 mg of aripiprazole
<i>Container:</i>	Injection vial
<i>Pack size:</i>	Single
<i>Approved therapeutic use:</i>	<i>For maintenance of clinical improvement in the treatment of schizophrenia.</i>
<i>Route of administration:</i>	Intramuscular (IM) injection
<i>Dosage:</i>	See Product information (PI, Attachment 1).
<i>ARTG numbers:</i>	211122 (300 mg) 211150 (400 mg)

### Product background

This AusPAR describes the application by the sponsor Lundbeck Australia Pty Ltd to register aripiprazole monohydrate (as Abilify Maintena) powder and solvent as a prolonged release suspension for injection in dosage strengths of 300 mg and 400 mg for the treatment of schizophrenia.

Nonclinical studies on the primary pharmacodynamics of aripiprazole suggest that its antipsychotic activity is mediated through a combination of partial agonism at dopamine D<sub>2</sub> and serotonin 5HT<sub>1A</sub> receptors and antagonism at serotonin 5HT<sub>2A</sub> receptors.

Other registered formulations of aripiprazole include Abilify tablets, orally disintegrating tablets and an immediate release injection.<sup>1</sup> Abilify Maintena will be presented in a therapeutic kit containing the components that are needed to reconstitute and administer the product into the gluteal muscle. Dosing is proposed as once monthly for this new intramuscular (IM) formulation.

The sponsor has proposed the following dosage and administration in their application:

*The recommended starting and maintenance dose of Abilify Maintena is 400 mg. Titration of the dose of Abilify Maintena is not required. Abilify Maintena should be administered by a healthcare professional once-monthly as a single injection (no sooner than 26 days after the previous injection). After the first Abilify Maintena injection, treatment should be in conjunction with 10 mg to 20 mg oral aripiprazole (or other oral antipsychotic) for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy. If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once-monthly should be considered.*

*For patients who have never taken oral or injectable aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with Abilify Maintena. When switching from oral antipsychotics, patients may continue their current oral antipsychotic (oral aripiprazole or prescribed dose of other oral antipsychotic) for 14 days following the first dose of Abilify Maintena to maintain therapeutic plasma concentrations during the initiation of Abilify Maintena. Abilify Maintena should then be administered once monthly as described above.*

*Inject immediately after reconstitution. Abilify Maintena should be administered by a healthcare professional once-monthly as a single injection (do not divide doses) into the gluteal muscle.*

Data was included in this application to support the addition of a new dosage form and dosage strengths to the currently approved Abilify presentations registered in Australia.

## Regulatory status

Aripiprazole was first included in the Australian Register of Therapeutic Goods (ARTG) as Abilify tablets in 2003 for the treatment of schizophrenia and was made available through the Pharmaceutical Benefits Scheme in 2004. Since 2003 additional dosage forms have been included in the ARTG and the treatment of bipolar disorder has been added as an indication (in 2011).

Marketing Authorisation Applications for Abilify Maintena were approved in the US on the 28 February 2013, in Canada on 10 February 2014 and in Switzerland on 28 April 2014 (see Table 1). Abilify Maintena was granted marketing authorisation via the European Union (EU) Centralised Procedure on 15 November 2013 by all 27 European Union member states, Norway, Liechtenstein and Iceland.

---

<sup>1</sup> Approved Indications for Abilify (aripiprazole) presentations in Australia; Abilify Tablets (2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg) and Abilify OroDispersible Tablets (10 mg, 15 mg, 20 mg and 30 mg): For the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy. Acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults as monotherapy and in combination with lithium or valproate; Maintenance treatment of manic or mixed episodes in Bipolar I Disorder in adults as monotherapy. Abilify Injection (9.75 mg solution for injection): For the treatment of agitation associated with schizophrenia.

## Product Information

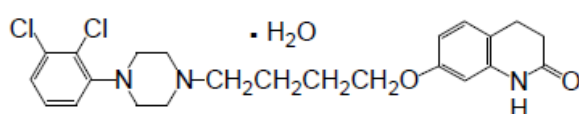
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

### Drug substance (active ingredient)

The chemical structure of aripiprazole monohydrate is shown below.

**Figure 1. Chemical structure.**



Molecular Formula  $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$ . Molecular Weight 466.40

There is a US Pharmacopeia monograph for aripiprazole.

Sterile aripiprazole monohydrate is manufactured by an aseptic process from anhydrous aripiprazole oral grade (intermediate). This application includes two sources of sterile Aripiprazole Monohydrate. Both manufacturers source oral grade Aripiprazole Anhydrous from the same source and produce the sterile monohydrate grade via aseptic filtration and recrystallization.

Sterile aripiprazole monohydrate is manufactured in a one-step sterile crystallization process starting with anhydrous aripiprazole. The critical quality attributes for sterile aripiprazole monohydrate are crystalline form and sterility. Desired crystalline form is the monohydrate. Product specific validation of the aseptic filtering and filling of the concentrated injection has been provided and was assessed by the TGA's Office of Laboratories and Scientific Services (see below).

### Drug product

Abilify Maintena is a single dose injectable suspension to be reconstituted with Water for Injections (WFI) prior to administration. The Water for Injections meets the current European Pharmacopeia (Ph.Eur) and USP.

The extended-release injectable suspension delivers 300 mg of aripiprazole in 300 mg/vial strength and 400 mg of aripiprazole in 400 mg/vial strength. The compositions of the 300 mg/vial and 400 mg/vial are the same differing only in the fill volume in the vial.

### Evaluation of sterility aspects

Following receipt of the sponsor's response to the questions raised in the evaluation of sterility aspects dated 30 August 2013, there were no objections from a microbiological viewpoint to the approval of the registration of Abilify Maintena (aripiprazole monohydrate) Powder and Solvent for Prolonged Release Suspension for Injection 300 mg and 400 mg.



## Biopharmaceutics

Absorption of aripiprazole from IM depot formulation was complete relative to IM standard formulation based on dose adjusted  $AUC_{(0-t)}$  values and maximum cumulative fraction of dose absorbed as determined by deconvolution analysis. Following single dose of aripiprazole in the IM depot formulation, the estimated time required to absorb 50% of the aripiprazole dose ranged between 10 to 35 days over the dose range of 15 to 400 mg. Single doses of aripiprazole IM depot over the range of 15 mg to 400 mg were generally safe and well-tolerated by subjects with schizophrenia or schizoaffective subjects.

## Quality summary and conclusions

The application and the supporting data relating to the composition, development, manufacture, quality control and stability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

There are no objections to registration from a quality and biopharmaceutics perspective.

The following details relate to this submission:

- A shelf life of 36 months when stored below 30°C with the extra condition '*Do not freeze*' has been assigned to the un-constituted powder for suspension for injection packaged in a 10 mL clear Type I glass vial, stoppered with a teflon laminated chlorobutyl rubber stopper and sealed with an aluminium flip-off seal with either a yellow polypropylene flip-off top (300 mg) or a blue polypropylene flip-off top (400 mg).
- An identical shelf life has been allocated to the Water for Injections diluent packaged in a 2 mL clear glass vial, stoppered with a FluroTec® Plus laminated gray bromobutyl rubber stopper and sealed with an aluminium flip-off cap with plastic flip-off disc. This has been accepted by the applicant.
- A shelf life of 4 h when stored below 25°C with the extra condition '*Do not freeze*' has been assigned to the suspension for injection stored in the clear Type I glass vial after reconstitution in the supplied Water for Injections diluent.
- A (revised) PI document was not provided; instead, an assurance was given that this will be submitted with the sponsor comments in relation to the Second round evaluation reports.
- Amended mock-ups of the vial, carton and diluent labels were provided and these were considered acceptable.
- The Provisional ARTG records (PARs) have been checked by the applicant and their accuracy has been confirmed.
- Current evidence of acceptable Good Manufacturing Practice (GMP) is available for the sites nominated for the manufacture of the active pharmaceutical ingredient (API).
- Acceptable composite release and expiry specifications have been submitted for the finished products.
- The application for registration of Abilify Maintena included results from a Phase II study that established to the TGA's satisfaction that absorption of aripiprazole from the IM depot formulation was complete relative to an IM standard formulation based on dose adjusted area under the concentration versus time curve from time 0 to time t ( $AUC_{(0-t)}$ ) values and the maximum cumulative fraction of dose absorbed as determined by deconvolution analysis. Following a single dose of aripiprazole in the

IM depot formulation, the estimated time required to absorb 50% of the aripiprazole dose ranged between 10 to 35 days over the dose range of 15 to 400 mg.

See also the Delegate's Overview below.

### **III. Nonclinical findings**

#### **Introduction**

The general quality of the submitted nonclinical studies was reasonable, although there was limited rationale for the nonclinical testing strategy and limited interpretation and analysis of the study results. A mix of previously evaluated nonclinical studies and new nonclinical studies was submitted.

The range of studies was consistent with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Pivotal studies examining repeat-dose toxicity were conducted under Good Laboratory practice (GLP) conditions with the proposed aripiprazole IM depot formulation. The exposure ratios are adequate to address the clinical relevance of the observed toxicities.

#### **Pharmacology**

##### **Mechanism of action**

Previously evaluated studies on the primary pharmacodynamics of aripiprazole suggest that its antipsychotic activity is mediated through a combination of partial agonism at D<sub>2</sub> and 5HT<sub>1A</sub> receptors and antagonism at 5HT<sub>2A</sub> receptors.

##### **Pharmacology and pharmacodynamic drug interactions**

Two older ex vivo studies, but no new recent studies, were submitted. These two ex vivo studies conducted on the mouse forebrain dopamine autoreceptor confirmed the dopamine autoreceptor agonist activity of aripiprazole. No new in vivo studies were submitted.

##### **Safety pharmacology**

One older study, but no new recent studies, was submitted. This study in guinea pigs showed aripiprazole had no effect on the corneal reflex indicating no local anaesthetic action.

##### **Pharmacokinetics**

Nonclinical pharmacokinetic studies with aripiprazole IM depot formulation were conducted in rats and dogs. Studies with aripiprazole IM aqueous formulation were conducted in mini-pigs, dogs and monkeys.

##### **Absorption**

Absorption following single dose administration of aripiprazole IM depot formulation in rats was dose-proportional with a long time to peak plasma concentration (T<sub>max</sub>) (168 h) and a long plasma half-life, in contrast to the aripiprazole IM aqueous formulation which

had a short  $T_{\max}$  (0.25 h) and short half-life. In mini-pigs, aripiprazole in IM aqueous formulation was completely bioavailable and showed wide tissue distribution. In dogs, absorption following IM depot formulation was dose-proportional with a  $T_{\max}$  of 8 h. In repeat-dose studies in rats and dogs, exposure was dose-proportional and increased with the period of exposure. There were no differences between the sexes.

### **Distribution**

Plasma protein binding of aripiprazole was previously shown to be high in humans and rats. Following IM depot formulation administration in rats, there was high retention of aripiprazole in the injection site muscle compared with the IM aqueous formulation. Tissue distribution following IM aqueous formulation was high at 0.25 h and radioactivity was still detected at 168 h in Harderian gland, submaxillary gland, liver, adrenal gland and kidney. As shown previously, aripiprazole can cross the blood-brain barrier and, following IM administration, was detected in the cerebellum at 0.25 h but not at 168 h postdose. Unchanged aripiprazole was the major substance at the injection site and in plasma (>85%).

### **Metabolism**

The metabolism of aripiprazole following oral administration was examined previously. No new metabolites have been identified in plasma over 1008 h following IM depot administration of aripiprazole in rats. At the injection site in the muscle tissue of rats, the two very minor High-performance liquid chromatography (HPLC) peaks (<0.6%), one identified as DM-1452 and the other possibly as an oxidation product, increased only slightly over 1008 h and were not considered to indicate the formation of new metabolites at the injection site. In mini-pigs, the AUC ratio of the pharmacologically active metabolite OPC-14857 (dehydro-aripiprazole) to aripiprazole was similar following intravenous (IV), IM and subcutaneous (SC) routes but higher following the oral route due to first-pass metabolism.

### **Excretion**

The major excretion route in rats following IM aqueous formulation administration was faecal (92%), with urinary excretion at 5 to 6% over 168 h. Similar results were obtained following oral administration in rats, with evidence of significant biliary excretion. In humans and monkeys, biliary excretion was evident after oral administration, together with urinary excretion.

### **Conclusion**

The submitted data on the pharmacokinetics of IM depot formulation demonstrated the high retention of aripiprazole at the injection site and its slow release into the plasma. There was no evidence of significant metabolism at the injection site. Once absorbed, it was distributed, metabolised and excreted similarly to orally administered aripiprazole, as examined previously. A similar pharmacokinetic pattern was observed in all species examined.

### **Toxicology**

#### **Acute toxicity**

Single-dose toxicity studies with the IM formulation have been conducted in two studies in dogs up to 400 mg/animal in 1 to 4 injections. In one study, there was evidence of tremors

and decreased activity on the treatment day but not on subsequent days. There were no other treatment related clinical signs. There was white discoloration and minimal to moderate granulomatous inflammation at the injection site which was still evident after 6 weeks, although reduced in severity. There was no evidence of muscle necrosis. Minimal changes in clinical pathology parameters that were evident upon treatment were not evident 4 weeks after dosing. The maximum non-lethal clinical dose was 400 mg/animal IM. Based on these studies, aripiprazole has a low order of acute toxicity via the clinical (IM depot formulation) route.

### Repeat-dose toxicity

Appropriately designed repeat dose toxicity studies with weekly treatment with aripiprazole IM depot formulation were conducted in rats up to 26 weeks and in dogs up to 52 weeks, consistent with relevant ICH guidelines. Two studies in monkeys with daily treatment with aripiprazole IM aqueous formulation over 2 and 4 weeks were also conducted.

### Relative exposure

Exposure ratios have been calculated based on animal: human plasma  $AUC_{0-28d}$  (see Table 2). The human reference value is from Clinical Trial 31-05-244. The No Observable Adverse Effect Level (NOAEL), if established, is shown in bold type in Table 1.

It is noted that the clinical exposure to aripiprazole associated with the maximum recommended human dose (MRHD) (400 mg/month) of Abilify Maintena ( $AUC_{0-28d}$  value  $163 \mu\text{g}\cdot\text{h}/\text{mL} = AUC_{0-24h}$   $5821 \text{ ng}\cdot\text{h}/\text{mL}$ ) is lower than the corresponding exposure associated with the MRHD (30 mg/day) of Abilify tablets ( $AUC_{0-24h}$   $7561\text{-}8360 \text{ ng}\cdot\text{h}/\text{mL}$ ; Clinical studies 31-93-204, 31-99-224). Thus, the toxicological risk assessment undertaken for aripiprazole in the nonclinical evaluation of the submission to register Abilify tablets is considered to be valid for the current submission, insofar as the overall toxicological profile of the compound is concerned. The main focus of the current nonclinical assessment is therefore the new formulation/route of administration.

**Table 1. Relative exposure in repeat-dose toxicity studies**

Species	Study duration	Dose mg/kg/ week IM	$AUC_{0-7d}$ ng·day/mL m/f	$AUC_{0-28d}^{\wedge}$ $\mu\text{g}\cdot\text{h}/\text{mL}$ m/f	Exposure ratio <sup>#</sup> m/f
Rat (SD)	26 weeks	25	728/647	70/62	0.43/0.38
		50	598/536	57/51	0.35/0.32
		100	3840/4336	368/416	2.26/2.55
Dog (Beagle)	26 weeks	10	365/265	35/25	0.22/0.16
		20	654/727	63/70	0.39/0.43
		40	1430/1520	137/146	0.84/0.90
	52 weeks	10	400/357	38/34	0.24/0.21
		20	833/693	80/66	0.49/0.41

Species	Study duration	Dose mg/kg/ week IM	AUC <sub>0-7d</sub> ng·day/mL m/f	AUC <sub>0-28d</sub> <sup>^</sup> µg·h/mL m/f	Exposure ratio <sup>#</sup> m/f
		40	2460/1820	236/175	1.45/1.07
Human*	5 months	400 mg	-	163	-

\*Schizophrenia patients stabilized on 10mg oral aripiprazole for at least two weeks before IM depot formulation administration. <sup>^</sup>Converted from AUC<sub>0-7d</sub> <sup>#</sup> animal: human plasma AUC<sub>0-28d</sub>

### Major toxicities

The nonclinical toxicity associated with aripiprazole IM depot formulation was largely restricted to effects observed at the injection site in rats and dogs. Other adverse effects were observed in the mammary gland, uterine cervix and vagina in rats. In monkeys treated with aripiprazole aqueous formulation, in addition to effects at the injection site, there was evidence of central nervous system (CNS) effects.

Local inflammation at the injection site was observed in all species. Changes observed included the occurrence of white or discoloured foci, which were interpreted as deposition of the drug, together with granulomatous inflammation. In rats, the number of foci was dose-related and decreased during the recovery period but foci were still present at the high dose level (100 mg/kg/week, equivalent to 2.4 times the clinical exposure, based on AUC) in both males and females at the end of the recovery period. There was no evidence of muscular necrosis.

In dogs, there was slight granulomatous inflammation at the injection site at all dose levels in both the 26 and 52 week studies but there was significant reduction during the recovery period and no inflammation was evident in the 52 week study following the 26 week recovery period at 40 mg/kg/week (equivalent to 1.45/1.07 (male/female) times the clinical exposure based on AUC). Slight muscle necrosis was observed in one high dose female animal, possibly related to local ischemia, which reversed during the recovery period. In monkeys treated with aripiprazole IM aqueous formulation over 4 weeks, there was evidence of mild/moderate inflammation and muscle necrosis at all dose levels up to 7.5 mg/kg/day (exposure not compared to the clinical exposure due to use of the aqueous formulation). After recovery, there was no necrosis and significantly reduced inflammation. The local inflammatory effects at the injection site are considered to be clinically relevant. The animal/human systemic exposure ratios achieved were not high, although it is likely that the limitation imposed by the physical size of the muscle at the administration site in the test species would have constrained further dose escalation, and in any event the rationale for these studies was to document the local effects of the depot injection rather than re-investigate the systemic toxicity of aripiprazole.

Mammary gland development was increased in rats at ≥25 mg/kg (equivalent to 0.4 times the clinical exposure based on AUC). Histopathology indicated mammary gland hyperplasia, hypertrophy of corpora lutea in the ovary, mucification of the epithelium of the uterine cervix and vagina. These changes were considered to be related to the pharmacological action of aripiprazole (D<sub>2</sub> partial agonistic activity), and have been extensively documented in previous nonclinical studies submitted to the TGA. These effects were not observed in dogs at 40 mg/kg (equivalent to 1.45/1.07 (male/female) times the clinical exposure based on AUC). These effects on the mammary gland may be clinically relevant.

Organ weight decreases were noted at 50 and 100 mg/kg in rats but these changes were reversed at the end of the recovery period. No organ weight changes were noted in dogs at

clinically relevant doses. These organ weight changes were not considered clinically relevant.

Decreased activity and an increase in tremors, indicative of CNS effects, were observed in monkeys immediately following dosing but not during the recovery period. These effects were considered to be secondary to the pharmacological activity of aripiprazole. These effects were not observed in dogs at 40 mg/kg (equivalent to 1.45/1.07 (male/female) times the clinical exposure based on AUC). These CNS effects may be clinically relevant.

In summary, the nonclinical data for the current submission have not identified any new systemic toxicities of aripiprazole, and the clinical systemic exposure is lower than for the oral products. The nonclinical observations of most relevance are the local tolerance findings.

### **Genotoxicity and carcinogenicity**

The genotoxic and carcinogenic potentials of aripiprazole were investigated during the nonclinical evaluation of the submission for oral administration.

Aripiprazole was clastogenic in *in vitro* assays in Chinese hamster lung cells but the overall profile from a comprehensive genotoxicity test battery was considered to be negative. The recent publication of Picada *et al* (2011)<sup>2</sup> reported a positive result in a Comet assay (deoxyribonucleic acid (DNA) damage) and a negative result in a micronucleus test, both in mice. A production intermediate and metabolite of aripiprazole, 2,3-DCPP, was positive in a chromosome aberration study in Chinese hamster lung cells (as aripiprazole is), although the result was considered likely to be secondary to cytotoxicity rather than to direct DNA reactivity. Thus, the original conclusion is still considered valid and no further examination of the genotoxicity of aripiprazole IM depot formulation is considered necessary.

In relation to carcinogenicity, a 70 week oral toxicity study in rats was provided, in which the adrenocortical tumorigenic response observed in female rats treated with aripiprazole for up to 2 years was further investigated. The results indicate that this tumorigenic response was a consequence of increased cell proliferation rather than due to reduced glucocorticoid output. This study supports the conclusion of the previous evaluation. No further carcinogenicity studies were considered necessary with the IM depot formulation, given the lower human exposure with the IM depot formulation compared with the oral formulation.

### **Reproductive toxicity**

The reproductive and developmental toxicity potential of aripiprazole was investigated during the nonclinical evaluation of the submissions for oral and aqueous IM formulations of aripiprazole. There was some possible evidence of teratogenicity at maternotoxic exposure levels in rats or rabbits which considerably exceeded the clinical exposure levels. Embryotoxicity indicative of growth retardation was evident in both species at the high exposure levels. Exposure (based on AUC) following oral or IV administration exceeded exposure following administration of IM depot formulation and exposure from all administration routes in animals exceeded the clinical exposure level. Therefore, no further reproductive studies were considered necessary with the IM depot formulation.

---

<sup>2</sup> Picada JN, Dos Santos BJN, Celso F, Monteiro JD, Da Rosa KM, Camacho LR, Vieira LR, Freitas TM, Da Silva TG, Pontes VM, Pereira P (2011) Neurobehavioural and genotoxic parameters of antipsychotic agent aripiprazole in mice. *Acta Pharmacologica Sinica*, 32, 1225-1232

### ***Pregnancy classification***

The sponsor has proposed pregnancy Category C<sup>3</sup>. The nonclinical reproductive toxicity data are more supportive for Category B3<sup>4</sup>. However, there are postmarket clinical data (described in the PI) supportive of Category C, and the oral Abilify products are Category C, so Category C would be appropriate for Abilify Maintena.

### **Local tolerance**

A range of studies examining local tolerance to IM aripiprazole was conducted in rats, rabbits, dogs and monkeys. The nonclinical testing was in general accord with the relevant guideline<sup>5</sup>. A series of exploratory studies (not reported in detail) identified aripiprazole formulations in carboxymethylcellulose (CMC), hydroxypropyl cellulose (HPC) or 15% Captisol® (sulfobutylether-beta-cyclodextrin) as having better local tolerance than other formulations. In the main studies (CMC formulation), swelling and granulomatous inflammation was evident in all species after IM administration, which persisted for weeks: at least 45 days (rats), 57 days (rabbits) and 29 days (monkeys), with some (but incomplete) recovery during the allocated posttreatment observation periods. CMC and Captisol® vehicles gave comparable local reactions. Systemic exposure was measured in the local tolerance studies, although the local effects rather than the known systemic toxicity of aripiprazole were of primary relevance. The local irritation effects at the injection site in the nonclinical studies are considered clinically relevant and the nonclinical evaluator recommended a thorough assessment of local tolerance in the clinical data.

### **Other studies**

#### ***Dependence***

A study in monkeys over 7 days did not produce any evidence of an increased frequency of self-administration of aripiprazole by infusion following self or forced administration. Aripiprazole was considered to possess 'no reinforcing effect'.

#### ***Phototoxicity***

In Balb/c3T3 mouse cells, aripiprazole did not influence the uptake of neutral red dye in the presence or absence of ultraviolet A (UVA) and was considered to have no phototoxic potential.

#### ***Juvenile toxicity and paediatric use***

Oral juvenile toxicity studies have been performed in rats for up to 2 months and in dogs for up to 6 months. The changes attributed to treatment were consistent with those previously reported for adult animals. In rats, CNS related effects and decreased body weight gain were observed at  $\geq 20$  mg/kg/day, attributed to the pharmacological activity of aripiprazole. Pathological changes were noted in various organs but were reversible and considered pharmacologically mediated. Neuropathology on the brain did not indicate any treatment related effects. Sexual maturation was delayed at  $\geq 20$  mg/kg/day but

---

<sup>3</sup> Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

<sup>4</sup>Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

<sup>5</sup> CPMP/SWP/2145/00 Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products Effective 10 January 2002.

subsequent sexual performance and reproductive parameters were normal. In dogs, CNS related effects and decreased body weight gain were observed at  $\geq 10$  mg/kg/day. These effects were reversible and no adverse pathological changes were observed in the nervous system or in other organs. There were no comparable long term studies in adult dogs. The CNS related effects, decreased body weight gain and pathological organ changes in juvenile animals may be clinically relevant.

These studies are not directly relevant to this submission, as aripiprazole is not currently approved for paediatric use and there is no proposal at present to extend the patient group to include patients of less than 18 years.

### Nonclinical summary and conclusions

- The nonclinical data provided were adequate to analyse and assess the nonclinical pharmacological, pharmacokinetic and toxicological properties of the IM depot form of aripiprazole in relation to its proposed clinical use. The data were in general accordance with the ICH guidelines. The pivotal studies were GLP compliant and conducted with the proposed clinical formulation. The exposure ratios are adequate to address the clinical relevance of the observed toxicities.
- Previously evaluated primary pharmacology studies and two additional studies established that its antipsychotic activity is mediated through a combination of partial agonism at D2 and 5HT1A receptors and antagonism at 5HT2A receptors.
- Previously evaluated studies adequately evaluated the safety pharmacology of aripiprazole. An additional safety pharmacology study in guinea pigs demonstrated that aripiprazole has no local anaesthetic action.
- The pharmacokinetic studies indicate that absorption of aripiprazole is slow and prolonged following administration of the IM depot formulation, with a T<sub>max</sub> of 168 h in rats and a long plasma half-life. In repeat dose studies, absorption was dose proportional and similar for both sexes. There was high retention of aripiprazole in the injection site muscle following administration of IM depot formulation. By contrast, aripiprazole was rapidly absorbed and showed wide tissue distribution following administration of IM aqueous formulation. The major substance at the injection site and in plasma was unchanged aripiprazole, with no evidence of the formation of new metabolites at the injection site following administration of the IM depot formulation. In mini-pigs, the AUC ratio of the pharmacologically active metabolite dehydro-aripiprazole (OPC-14857) to aripiprazole was similar following administration by IV, IM and SC routes. Excretion following IM depot formulation was not examined but following IM aqueous formulation, faeces was the major excretion route (92%), as it was following oral administration.
- In single dose toxicity studies in dogs with IM depot formulation up to 400 mg/animal, there were transitory CNS effects on day one only, together with minimal to moderate granulomatous inflammation at the injection site which reduced in severity with time but was still evident after 6 weeks. There was no evidence of muscle necrosis.
- Repeat dose studies in rats and dogs with IM depot formulation consistently produced local inflammation at the injection site. Similar effects were seen in monkey with IM aqueous formulation. Inflammation was accompanied by the occurrence of white foci, considered to be deposition of aripiprazole crystals. The number of foci and inflammation severity decreased during the recovery period. Systemic effects observed in rats were considered to be related to the pharmacological action of aripiprazole (mammary gland hyperplasia, hypertrophy of the corpora lutea, mucification of the uterine cervix and vagina epithelium). These effects were observed below the clinical exposure in rats, but were not observed in dogs at the clinical



exposure. In monkeys, decreased activity and an increase in tremors were observed after dosing with IM aqueous formulation, which may be clinically relevant.

- Previous studies indicated an overall non genotoxic profile for aripiprazole, confirmed by recent studies (Comet assay, micronucleus test). No further examination of genotoxicity of the aripiprazole IM depot formulation was considered necessary.
- A 70 week oral study confirmed that the adrenocortical tumorigenic response observed in a previous rat carcinogenicity study was a consequence of increased cell proliferation rather than to a reduced glucocorticoid output. No further carcinogenicity studies were considered necessary with the IM depot formulation, given the lower human exposure with the IM depot formulation compared to the oral formulation.
- Previous reproductive and developmental toxicity studies found some possible evidence of teratogenicity, although growth retardation was evident at exposures well in excess of the clinical exposure. As exposure following IM depot formulation was lower than exposure following oral administration, no further reproductive studies were considered necessary with the IM depot formulation. The sponsor has proposed pregnancy Category C, consistent with the oral Abilify® products and postmarket reports and this is supported.
- Local tolerance studies in rats, rabbits, dogs and monkeys confirmed that aripiprazole IM depot formulation produced swelling and granulomatous inflammation in all species. These effects may be clinically relevant and local tolerance in patients will require assessment.
- Aripiprazole is not approved for paediatric use. Juvenile toxicity studies in rats and dogs produced a range of toxicities related to its pharmacological activity. These toxicities have been previously observed in adult animals, and may be clinically relevant.

### **Nonclinical conclusions and recommendation**

- There were no major deficiencies in the nonclinical dossier.
- The new primary pharmacology data were consistent with previous studies attributing the antipsychotic activity to actions at various receptor subtypes. Safety pharmacology data on aripiprazole were adequately evaluated previously. No additional pharmacology data specifically using the IM depot formulation are necessary.
- The pharmacokinetics of the IM depot formulation indicated high retention in the injection site muscle, with no evidence of formation of new metabolites.
- Repeat dose and local tolerance studies with the IM depot formulation reported inflammatory effects at the injection site, with some evidence of posttreatment recovery. The known systemic effects of aripiprazole were also confirmed.
- There are no changes to the previously documented genotoxicity and carcinogenicity profiles and no additional genotoxicity or carcinogenicity data specifically using the IM depot formulation are necessary.
- The reproductive and developmental toxicity of aripiprazole was adequately evaluated previously. Given the lower exposure from the IM depot formulation, no additional studies using the IM depot formulation are necessary. Pregnancy Category C is appropriate.

- Based on the nonclinical data evaluated herein, there are no nonclinical objections to the registration of aripiprazole IM depot formulation as proposed.
- The nonclinical evaluator recommended amendments to the draft Product Information document but the details of these are beyond the scope of this AusPAR.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### Clinical rationale

Non-adherence to treatment has been identified as a major risk factor for relapse in schizophrenia; it is estimated that approximately 50% of patients miss taking 30% or more of their medications for schizophrenia. Limited data comparing oral and depot formulations suggest that depot formulations may have an advantage over oral antipsychotics for relapse prevention and rates of hospitalisation.<sup>6</sup>

#### Guidance

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use
- pp. 121 - 125 of Rules 1998 (3C) - 3CC5a The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions  
Adopted by the TGA with the following conditions:

Attention is drawn to:

- Applicability, Section 7, which states that circumstances exist in which the Guidelines may not be applicable. It should be noted that the listing of exceptional circumstances is not exhaustive. Sponsors should give careful attention to whether, in any particular instance, the clinical safety of the product would be adequately supported by the numbers of subjects proposed, and
- Supplementary data, Section 8 is NOT ADOPTED. To permit decisions within legislated timeframes, the sponsor should include in the initial submission all clinical safety data necessary to support registration
- CPMP/EWP/559/95 Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia.
- CPMP/EWP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia.

---

<sup>6</sup> Sponsor's Clinical Overview.

## Contents of the clinical dossier

### *Scope of the clinical dossier*

There were 34 studies referred to in the submission that had been previously submitted<sup>7</sup> but were not included with this submission:

The submission contained the following clinical information:

#### *Clinical pharmacology studies:*

- CN138-020 - Assessment Of The In Vivo Release Characteristics And Safety Of An Intramuscular Depot Formulation Of Aripiprazole In Subjects With Schizophrenia Or Schizoaffective Disorder
- 31-07-002 - Assessment of the Safety, Tolerability, and Pharmacokinetics of Aripiprazole IM Depot Formulation by Single Administration in Patients with Schizophrenia - A multicenter, uncontrolled, open-label, single-dose trial of OPC-14597 IMD
- 31-05-244 - An Open-label, Parallel Arm, Multiple Dose Tolerability, Pharmacokinetics and Safety Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole Intramuscular Depot Formulation Once Every Four Weeks
- 31-11-289 - An Open-label, Safety and Tolerability Trial of Aripiprazole IM Depot Treatment Initiation in Adult Subjects With Schizophrenia Stabilized on Atypical Oral Antipsychotics Other Than Aripiprazole
- 031-10-002 - Open-label, multicenter, multiple-dose trial to investigate the pharmacokinetics of aripiprazole IM depot (OPC-14597IMD) in patients with schizophrenia<sup>8</sup>
- CN138-402 - Effects of Aripiprazole On the Steady-State Pharmacokinetics of Lamotrigine In Subjects with Bipolar I Disorder<sup>9</sup>
- CN138-139: Assessment of the potential for drug-drug interactions between aripiprazole and five antidepressants in a multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of aripiprazole as adjunctive therapy in the treatment of patients with MDD<sup>10</sup>

#### *Population pharmacokinetic analyses:*

- 31-11-287 - Population pharmacokinetic modelling for the aripiprazole IM depot formulation as maintenance treatment in subjects with schizophrenia
- 31-12-292 - Aripiprazole Validation of a Previously Developed Population Pharmacokinetic Model for Aripiprazole IM Depot Formulation as Maintenance Treatment in Subjects With Schizophrenia Using Data From Protocol 31-07-247

#### *Pivotal efficacy/safety studies:*

- 31-07-246 - A 52-week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot

---

<sup>7</sup> Of these 31-98-208 and CN38-022 were incomplete in that submission.

<sup>8</sup> A protocol synopsis only was submitted with no results

<sup>9</sup> This study treatment comprised aripiprazole tablets (10 to 30mg/day), for 14 days and to patients with a diagnosis of Bipolar I Disorder, who were clinically stable on lamotrigine that is, not relevant to this submission to register a different formulation with a different Indication.

<sup>10</sup> This study treatment comprised Aripiprazole, 2mg and 5mg tablets, flexibly dosed (2mg, 5mg, 10mg, 15mg, and 20mg once daily) for 6 weeks and to patients with a diagnosis of major depressive disorder, that is, not relevant to this submission to register a different formulation with a different Indication.

### Formulation of Aripiprazole as Maintenance Treatment in Patients with Schizophrenia "ASPIRE US"

- 31-07-247 - 38-week, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole as Maintenance Treatment in Patients with Schizophrenia<sup>11</sup> "ASPIRE EU"

#### *Other efficacy/safety studies.<sup>12</sup>*

- 31-08-003 - A Multicenter, Active-controlled Double-blind, Parallel Group-comparison Trial to Investigate the Efficacy and Safety of Aripiprazole IM Depot (OPC-14597IMD) Compared with Aripiprazole Tablets in Patients with Schizophrenia
- 31-08-248 - A 52-week, Multicenter, Open-label Study to Evaluate the Effectiveness of Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients with Schizophrenia "ASPIRE OPEN-LABEL" (Aripiprazole Intramuscular Depot Program in Schizophrenia)
- 31-11-283 - A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects with Schizophrenia Treated Prospectively for 6 Months with Aripiprazole IM Depot Compared with 6-month Retrospective Treatment with Oral Antipsychotics in a Naturalistic Community Setting in the US
- 31-10-270 - An Open-Label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia
- 31-11-284 - A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects with Schizophrenia

*Periodic Safety Update Reports (PSURs) 17 Jul 2002 to 16 Jul 2012, Integrated Summary of Efficacy, Integrated Summary of Safety.*

### **Paediatric data**

The submission included EU approval of a paediatric investigation plan deferral (for tablets, orodispersable tablets, and oral solution for oral use) and a waiver (for solution for injection, and powder for suspension for injection for intramuscular use [Abilify Maintena]). The submission did not include paediatric data.

### **Good clinical practice**

All trials in the clinical program for aripiprazole IM depot were conducted in compliance with Good Clinical Practice (GCP).<sup>13</sup>

### **Pharmacokinetics**

#### **Studies providing pharmacokinetic data**

New studies in healthy adults were not undertaken which, considering the long half-life of the formulation, is not unreasonable.

<sup>11</sup> This study had its primary endpoint (and hence primary objective and non – inferiority margin) amended almost 3 years into the trial.

<sup>12</sup> These studies looked at various aspects of efficacy but were not completed so were submitted for safety data only.

<sup>13</sup> Sponsor's Clinical Overview

Table 2 shows the studies relating to each pharmacokinetic (PK) topic and the location of each study summary.

**Table 2. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
PK in healthy adults	There were no new studies submitted		
PK in schizophrenic patients	General PK - Single dose	CN138-020	
		31-07-002	*
		31-11-289	*
	Multi-dose	31-05-244	*
		31-07-246	
		31-07-247.	
	Bioequivalence† - Single dose	CN138-020	*
PK in special populations	Renal impairment – oral	31-98-208	*
Population PK analyses	Healthy subjects and Target population	31-11-287	*
	Target population	31-12-292	*

\* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

Table 3 lists PK studies that were excluded from consideration due to study deficiencies. Further details of PK and Population PK can be found in Attachment 2.

**Table 3. Pharmacokinetic studies excluded from consideration.**

Study ID	Indication	Formulation
31-10-002	schizophrenia	IM depot
CN138-139	MDD	oral
CN138-402	Bipolar I Disorder	oral

## Evaluator's conclusions on pharmacokinetics

### Guidance

CPMP/EWP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia.

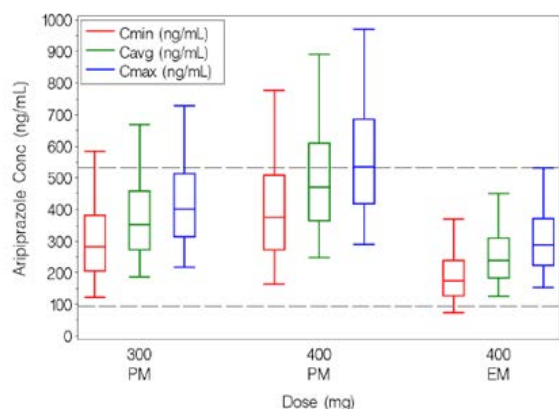
- Of specific interest is the comparison of the concentration time curves after administration of the oral formulation and the depot formulation over the dosing range. This comparison should be used for an adequate dose and dose interval selection of the depot formulation.
- Depending on the type of formulation, the influence of volume, amount and concentrations injected (dose proportionality), or other circumstances (like exercise), on the release characteristics should be discussed or investigated especially with respect to the possibility of dose dumping.
- As the parenteral administration of a depot formulation will release the drug slowly compared to oral formulation, the time to achieve steady state concentration after switching from oral to parenteral treatment should be taken into consideration especially with respect to the efficacy.
- Special attention should be paid to the first pass elimination of the active substance as this may be substantially different between the two routes of administration.

### ***Evaluator's conclusions***

The PKs raise a number of concerns in regard to under and overdosing in poor and extensive metabolisers (see Figure 2).

**Figure 2. Comparison of Steady-State Exposure Measures for Poor Metabolisers, Stratified by IM Depot Dose**

EM= Extensive Metabolizer, PM= Poor Metabolizer  
Horizontal dashed lines represent the therapeutic range.



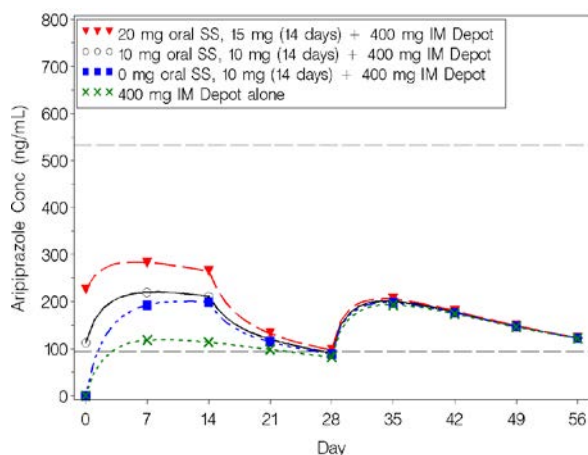
Steady state is reached by the fourth cycle at which stage even on 400 mg some extensive metabolisers will be at sub-therapeutic levels towards the end of the cycle, with presumably a greater number and for some a greater duration in the preceding months.

When steady state is reached even on 300 mg some poor metabolisers will be at above therapeutic levels throughout the cycle, while the likelihood of increased adverse events (AEs) does not directly affect therapy, the increased risk of discontinuation due to AEs does.

A single 400 mg IM depot dose is shown to achieve mean sub-therapeutic levels for the first and last 3 days of the initial treatment cycle, presumably extensive metabolisers will fare worse (see Figure 3).

### Figure 3. Median Concentration versus Day for First 2 Doses, Stratified by Dosing Initiation Scheme

Horizontal dashed lines represent the therapeutic range.



Bioequivalence was not shown. Relative bioavailability based on AUC ranged from 0.90 to 1.44 with the smallest CV 19.85%. While relative exposure based on  $C_{max}$  was only 0.04-0.07.

### Pharmacodynamics

There were no new pharmacodynamic (PD) studies included with this submission.

### Dosage selection for the pivotal studies

Based on the assessed pharmacokinetic (PK) parameters from Trial CN138-020 and from previous oral steady state studies aripiprazole plasma concentration-time profiles were simulated. These simulations included a proposed switching regimen in which oral dosing was tapered off with concomitant administration of 100, 200, 300, and 400 mg aripiprazole IM depot monthly (that is, every 28 days). Data from these simulations indicated that the lower 95% confidence interval (CI) for minimum plasma concentration ( $C_{min}$ ) for 400 mg/300 mg aripiprazole IM depot would be expected to be above (or very close to) the steady-state  $C_{min}$  of daily dosing with aripiprazole 10 mg and below the mean steady-state maximum plasma concentration ( $C_{max}$ ) of daily dosing with aripiprazole 30 mg at all times, including tapering off oral dosing.

Trial 31-05-244 showed that once monthly administration of the 200 mg IM depot injections did not result in mean aripiprazole trough plasma concentrations that were comparable to the therapeutic concentrations of 10 mg to 30 mg oral aripiprazole administered daily to schizophrenic subjects. In this multiple dose trial and in another single dose trial (Trial CN138-020), the PK profiles and clinical data for aripiprazole IM depot 400 mg/300 mg suggested that these doses would be efficacious and tolerable, and thus, both were further investigated in the Phase III trials.

### Efficacy

#### Studies providing efficacy data

Pivotal efficacy/safety studies submitted included:

- Trial 31-07-246 - A 52-week, Multi-centre, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular

### Depot Formulation of Aripiprazole as Maintenance Treatment in Patients with Schizophrenia "ASPIRE US"

- Trial 31-07-247 - 38-week, Multi-centre, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole as Maintenance Treatment in Patients with Schizophrenia<sup>14</sup> "ASPIRE EU"

Other efficacy data were also included (see *Scope of the clinical dossier* above).

## Evaluator's summary of the clinical efficacy for the treatment of schizophrenia

### Guidance

*CPMP/EWP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia.*

- The efficacy and safety of the compound are known and it is not necessary to show this in itself for the depot formulation, provided no specific claims are made.
- It is of importance to know whether the new formulation affects efficacy or safety in comparison to the oral formulation.
- The purpose of the study is to show non-inferiority of the depot formulation versus the oral formulation. This can be done in various ways, for example, by showing that the situation at baseline is maintained or improved to the same extent or by using relapse/deterioration as endpoint.
- The results should demonstrate non-inferiority. The non-inferiority margin should be defined in advance and justified, taking into account among others, the available efficacy data and the patient population, the duration of the trial and the endpoint.
- Assay sensitivity needs to be addressed. One way to address this could be to include a placebo arm. Alternatively the trial could include various dose arms.
- Placebo, as an additional arm would ensure assay sensitivity but might be less feasible in this setting.
- Efficacy should be scored by using appropriate scales, the choice of which should be justified. Maintenance of effect can be assessed by comparing scores at baseline and end of the trial. Relapse/deterioration, expressed as number of patients relapsing and/or time to relapse is another option and might be a more sensitive.
- Duration of 3 months of the double blind maintenance period will be acceptable, depending on the inter-injection interval, but a longer duration (for example, 6 months) might increase the assurance that the study indeed has sufficient assay sensitivity.

*CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study*

The fundamental requirement on the Phase III documentation is that it consists of adequate and well-controlled data of good quality from a sufficient number of patients, with a sufficient variety of symptoms and disease conditions, collected by a sufficient

<sup>14</sup> This study had its primary endpoint (and hence primary objective and non – inferiority margin) amended almost 3 years into the trial.



number of investigators, demonstrating a positive benefit/risk in the intended population at the intended dose and manner of use.

The minimum requirement is generally one controlled study with statistically compelling and clinically relevant results.

Special attention will be paid to:

- The internal validity. There should be no indications of a potential bias.
- The external validity. The study population should be suitable for extrapolation to the population to be treated.
- Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.
- The degree of statistical significance. Statistical evidence considerably stronger than  $p < 0.05$  is usually required, accompanied by precise estimates of treatment effects, that is, narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified. When the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin.
- Data quality.
- Internal consistency. Similar effects demonstrated in different pre specified sub-populations. All-important endpoints showing similar findings.
- Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
- The plausibility of the hypothesis tested.

Details of Study 31-07-246 Aspire US and Study 31-07-247 Aspire EU can be found in Attachment 2.

### ***Evaluator's conclusions***

The submission rests for efficacy on 2 studies.

Study 31-07-246 was a comparison with placebo that by its interim analysis was able to show efficacy and in order to minimise exposure of participants to placebo was terminated after the interim analysis. Thus the sponsor says the requirements of efficacy for FDA registration were met.

At 3 months there were 123 patients on aripiprazole IM depot and 47 on placebo. PK data suggests steady state is reached by the fourth injection (that is, at the end of 3 months after the initial injection).

The interim analysis of efficacy data (which included 344 randomized subjects and 64 events of impending relapse - 50% of the projected total of 125 events), showed that time to impending relapse was significantly shorter for subjects on placebo compared to aripiprazole IM depot ( $p < 0.0001$ ; log-rank test). Accordingly the study was terminated, during the process of which an additional 16 impending relapse events occurred, thus the final efficacy analysis included 403 randomized subjects and 80 impending relapse events, 27/269 (10.0%) on aripiprazole IM depot and 53/134 (39.6%) on placebo.

The final analysis showed that the time to impending relapse was significantly shorter for subjects on placebo compared with subjects on aripiprazole IM depot ( $p < 0.0001$ ; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 5.029 (95% CI = 3.154, 8.018).

Study 31-07-247 was intended to compare efficacy of the IM depot with the oral formulation and ensure assay sensitivity by using various dose arms. However despite there not being provision for an interim analysis, some analysis was undertaken because, almost 3 years into the trial, the primary efficacy endpoint was changed because of a lower than anticipated relapse rate. As a result the primary efficacy endpoint was changed from *'time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 3'* to *'the proportion of subjects experiencing exacerbation of psychotic symptoms/impending relapse by end of 26 weeks of treatment from the date of randomization in Phase 3, in schizophrenic subjects who have maintained stability on oral aripiprazole for at least 8 consecutive weeks in Phase 2 of the study.'* Although not submitted there must have been a change to the primary objective too since it refers to the primary endpoint in specific terms. This also means that the non-inferiority margin was no longer predefined. The original primary endpoint failed to meet the non-inferiority margins.

The options this evaluator sees for Study 31-07-247 are

- To reject it on the basis that it has flawed methodology from changing the primary endpoint (and hence the primary objective) mid-study.
- To accept the methodology as constituting a new trial started mid study. This leaves the original study abandoned as a failure (it failed to achieve its primary endpoint anyway). It also requires a new population since one of the exclusion criteria precluded the use of the original trial participants in the new trial.<sup>15</sup> Even if this is overlooked, and the new trial is accepted as incorporating the original population as well, the 2 results (from the first part of the trial versus the second part of the trial) cancel each other for efficacy.

This evaluator believes the former, that is, that rejection on the basis of flawed methodology is the appropriate approach.

The other studies looking at various aspects of efficacy were incomplete at the time of submission and were submitted for evidence of safety. The PK comparison of oral and IM formulations while showing comparability of AUC, show very different  $C_{max}$  results as well as there being concerns of sub therapeutic concentrations.

The evidence of efficacy of the IM depot formulation thus rests on the single Study 31-07-246.

## **Safety**

### **Studies providing safety data**

The main safety data set was from pooling data from the double-blind phases of the 2 completed Phase III trials (Controlled Trials).

Pooled data from any of the aripiprazole IM depot schizophrenia trials (except Trial 031-08-003) was used to allow detection of rare events, (All Trials).

### **Patient exposure**

At the time of cut-off (2 April 2012):

---

<sup>15</sup> Subjects who received any investigational agent in a clinical trial within 30 days prior to screening or who were randomized into a clinical trial with aripiprazole IM depot at any time. NOTE: Subjects who discontinued at any phase of the trial (Conversion Phase to the Double-blind, Active-controlled Phase) were not eligible and could not be rescreened to enter the trial.

- Overall, 1,624 adult subjects with schizophrenia had received aripiprazole IM depot (15 to 400 mg)
- 1,539 subjects had received aripiprazole IM depot 400/300 mg
- 995 subjects have received  $\geq 7$  aripiprazole IM depot 400/300mg injections (that is, had been treated for  $\geq 6$  months)
- 784 subjects had received  $\geq 13$  injections (that is, have been treated for  $\geq 12$  months)
- 244 subjects have received  $\geq 26$  injections (that is, have been treated for  $\geq 24$  months).

See Tables 4 and 5 for summaries of patient exposure by number of consecutive injections and subjects having  $\geq 1$  injection, respectively.

**Table 4. Exposure to Aripiprazole IM Depot by Number of Consecutive Injections (Controlled Trials)**

Injection	Aripiprazole IM Depot 400 mg/300 mg (N = 534) n (%)	Oral Aripiprazole 10-30 mg <sup>a</sup> (N = 266) n (%)	Aripiprazole IM Depot 50 mg/25 mg (N = 131) n (%)	Placebo <sup>a</sup> (N = 134) n (%)
1st IM depot injection	534 (100)	266 (100)	131 (100)	134 (100)
2nd IM depot injection	474 (88.8)	244 (91.7)	120 (91.6)	101 (75.4)
3rd IM depot injection	434 (81.3)	226 (85.0)	110 (84.0)	77 (57.5)
4th IM depot injection	403 (75.5)	219 (82.3)	96 (73.3)	58 (43.3)
5th IM depot injection	365 (68.4)	208 (78.2)	85 (64.9)	50 (37.3)
6th IM depot injection	336 (62.9)	205 (77.1)	80 (61.1)	41 (30.6)
7th IM depot injection	303 (56.7)	199 (74.8)	72 (55.0)	31 (23.1)
8th IM depot injection	275 (51.5)	192 (72.2)	70 (53.4)	24 (17.9)
9th IM depot injection	262 (49.1)	185 (69.5)	66 (50.4)	19 (14.2)
10th IM depot injection	241 (45.1)	168 (63.2)	56 (42.7)	13 (9.7)
11th IM depot injection	37 (6.9)	NA	NA	10 (7.5)
12th IM depot injection	31 (5.8)	NA	NA	5 (3.7)
13th IM depot injection	25 (4.7)	NA	NA	5 (3.7)

a Matching placebo injection. NA = not applicable. Up to 10 injections in Trial 31-07-247 and up to 13 injections in Trial 31-07-246.

**Table 5. Extent of Exposure to Aripiprazole IM Depot: Subjects Having  $\geq 1$  Aripiprazole IM Depot Injection (All Trials)**

Number of subjects	ARIP- IMD < 300mg	ARIP- IMD 300- 400mg	ARIP- IMD 15- 400mg
Treated	168	1539	1624
Total aripiprazole IMD injections	948	21030	21978
Total days of exposure to aripiprazole IMD	26428	590702	617130
Total years of exposure to aripiprazole IMD (PEY) <sup>1</sup>	72.4	1617.3	1689.6

<sup>1</sup>PEY = Subjects total days of exposure to Aripiprazole IMD / 365.25

## Safety issues with the potential for major regulatory impact

### *Injection site reactions*

*Controlled Trials:* 37/534 (6.9%) subjects on IM depot 400/300 mg, 7/266 (2.6%) subjects on tablets, 1/131 (0.8%) subjects on IM depot 50/25 mg and 5/134 (3.7%) placebo subjects experienced AEs related to the injection site.<sup>16</sup> Injection site reactions reported by subjects on tablets included injection site pain (6/266, 2.3%), injection site erythema (3/266, 1.1%), and injection site induration and injection site swelling (each in 2/266, 0.8%). In the placebo group, injection site-related treatment emergent AEs (TEAEs) included injection site pain (5/134, 3.7%) and injection site erythema (1/134, 0.7%).

In the IM depot 50/25 mg group, injection site-related AEs included injection site pain (1/131, 0.8%). In the aripiprazole IM depot 400/300 mg group, injection site-related AEs included injection site pain (28/534 subjects, 5.2%), injection site induration (8/534, 1.5%), injection site swelling (3/534, 0.6%), injection site erythema (3/534, 0.6%), and injection site discomfort, injection site pruritis, injection site reaction and vessel puncture site pain (each in 1/534, 0.2%).

### *VAS scores and investigator assessments<sup>17</sup>*

Trial 31-07-247 Double-blind, Active-controlled Phase, the subjects mean VAS pain score on IM depot 400/300 mg was 5.6 after the first injection and 3.7 after the last, for subjects on tablets<sup>18</sup> mean VAS was 4.9 (first injection) and 3.5 (last injection), for IM depot 50/25 mg mean VAS was 3.3 (first injection) and 2.4 (last injection).

Investigators rated pain, redness, swelling, and induration with IM depot 400/300 mg as absent in 81.4% to 98.1% of subjects after the first injection and absent in 88.3% to 98.9% after the last injection, for subjects on tablets pain, redness, swelling and induration were absent in 83.3% to 98.5% (first injection) and 90.2% to 99.6% (last injection).

For IM depot 50/25mg they were absent in 90.7% to 99.2% (first injection) and 90.0% to 99.2% (last injection).

Trial 31-07-246 Double-blind, Placebo-controlled Phase, the subjects mean VAS pain score on IM depot 400/300mg was 5.1 after the first injection and 4.0 after the last, for placebo subjects mean VAS were 5.1 (first injection) and 4.9 (last injection).

Investigators rated pain, redness, swelling, and induration for subjects on IM depot 400/300mg, as absent in 80.1% to 98.1% of subjects after the first injection, and as absent in 84.4% to 98.5% of subjects after the last injection, for subjects on placebo was absent in 72.2% to 97.7% of (first injection) and 77.3% to 97.7% (last injection).

*All Trials:* 121/1539 (7.9%) aripiprazole IM depot 400/300mg subjects had AEs related to the injection site.

The overall incidence of AEs related to the injection site in subjects treated with aripiprazole IM depot 400/300 mg was 9.3% (108/1160) for subjects treated  $\geq$  3 months and 11.3% (25/221) for subjects treated  $\geq$  24 months.

There were increases in the incidence of the following injection site-related AEs in subjects with longer exposure to aripiprazole IM depot 400/300 mg injection site pain (95/1160 [8.2%] for subjects treated  $\geq$  3 months and 20/221 [9.0%] subjects treated for

<sup>16</sup> Subjects randomized to placebo and to oral aripiprazole received a placebo IM depot injection

<sup>17</sup> Within 30 minutes before and 1 hour ( $\pm$  15 minutes) after each IM depot injection and at each trial visit

<sup>18</sup> Subjects assigned to treatment with IM depot received oral matching placebo tablets, and those assigned to oral aripiprazole tablets received IM depot matching placebo (either high-dose IM depot placebo or low-dose IM depot placebo).

≥ 24 months) and injection site induration (12/1160 [1.0%] and 6/221 [2.7%], respectively).

### **Liver toxicity**

*Controlled Trial:* no potential Hy's Law cases were identified during the double-blind phase of either study.

One subject in Study 31-07-247 had laboratory results meeting the criteria for Hy's Law during the Oral Stabilization Phase, 2 days later, during the Double-blind, Active-controlled Treatment Phase, abnormal hepatic function was reported as a TEAE for this subject. This event resolved and was considered mild in severity and unrelated to trial medication. No action was taken regarding trial medication due to this event.

### **Suicide**

*Controlled Trials:* 6/534 (1.1%) subjects on IM depot 400/300 mg, 1/266 (0.4%) subjects on tablets, 3/131 (2.3%) on IM depot 50/25 mg and no placebo subjects had an AE that was considered related to suicidal ideation/suicide.

### **Increased weight**

*Controlled Trials* (see Table 7): Increased weight was a reported AE for 50/534 (9.4%) subjects on IM depot 400/300 mg, 35/266 (13.2%) subjects on tablets and 13/134 (9.7%) placebo subjects. Decreased weight was reported for 35/534 (6.6%) subjects on IM depot 400/300 mg, 16/266 (6.0%) subjects on tablets, and 4/134 (3.0%) placebo subjects.

**Table 6. Incidence of potentially clinically relevant weight gain and weight loss in double-blind, active-controlled phase (subjects treated in double-blind phase of Trial 31-07-247)**

Time Point Parameter	Aripiprazole IM Depot 400 mg/300 mg (N = 265)		Oral Aripiprazole 10-30 mg (N = 266)		Aripiprazole IM Depot 50 mg/25 mg (N = 131)	
	Ne <sup>a</sup>	n (%) <sup>b</sup>	Ne <sup>a</sup>	n (%) <sup>b</sup>	Ne <sup>a</sup>	n (%) <sup>b</sup>
At Last Visit						
Weight gain ≥ 7% <sup>c</sup>	264	25 (9.5)	266	31 (11.7)	131	6 (4.6)
Weight loss ≥ 7% <sup>c</sup>	264	27 (10.2)	266	12 (4.5)	131	13 (9.9)
Any Time During Phase						
Weight gain ≥ 7% <sup>c</sup>	264	42 (15.9)	266	43 (16.2)	131	8 (6.1)
Weight loss ≥ 7% <sup>c</sup>	264	40 (15.2)	266	27 (10.2)	131	18 (13.7)

<sup>a</sup> Ne is the total number of subjects with a post-baseline weight result at the visit. <sup>b</sup> n is the number of subjects meeting the criteria for potential clinical relevance. <sup>c</sup> Change from Double-blind, Active-controlled Phase baseline.

### **Convulsions**

*Controlled Trials:* 1/131 (0.8%) subjects on IM depot 50/25 mg and 1/134 (0.7%) placebo subjects had AEs of convulsions/seizures. No aripiprazole IM depot 400/300 mg subjects or tablets subjects had AEs of convulsions/seizures.

*All Trials:* 2/1539 (0.1%) aripiprazole IM depot 400/300 mg subjects had AEs related to convulsions/seizures within ≤ 3 months.

### **Hepatic impairment**

This had previously been studied with a single oral dose. No new studies with the IM depot were submitted. The sponsor comments '*Of note, in patients with severe hepatic impairment, the data available may be insufficient to establish recommendations. In these patients dosing should be managed cautiously; use of oral aripiprazole should be considered.*'

### **Renal impairment**

This had previously been studied with a single oral dose. No new studies with the IM depot were submitted. The Abilify PI states '*In patients with severe renal impairment (creatinine clearance < 30 mL/min), C<sub>max</sub> of aripiprazole (given in a single dose of 15mg) and*

*dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.'*

## **Evaluator's conclusions on safety**

### ***Guidance***

CPMP/EWP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia.

- It is of importance to know whether the new formulation affects efficacy or safety in comparison to the oral formulation.
- Product related and dose related adverse effects are known from the oral formulation but the database of the depot formulation should be checked for comparability and unexpected adverse effects.
- In addition local adverse effects should be assessed specifically.
- Timing of scoring of adverse effects should be justified, especially in case the plasma levels from each injection should exceed the corresponding levels from oral administration for a substantial part of the inter-injection interval.
- Depending on the type of formulation the possibility of a sudden increase in absorption and subsequently in side effects should be addressed.<sup>19</sup>
- Data over a 6 month period will usually be sufficient but this might depend on the length of the inter-injection interval.

### ***Evaluator's conclusions***

In the controlled studies injection site reactions were greater (6.9%) with IM depot 300/400 mg than with the placebo used with (2.6%) or without (3.7%) oral tablets and they appeared to be dose related (0.8% on 25/50mg IM depot).

In the controlled trials suicidal ideation/suicide appeared greater (1.1%) with IM depot 400/300 mg than on tablets (0.4%).

Otherwise the AEs were comparable.

The dosing gap appears to be appropriate in terms of incidence of AEs.

There is sufficient duration of safety exposure.

The lack of safety data in the elderly is of concern, particularly as the number of subjects with serious AEs (SAEs) were greater with increased age > 45 years and discontinuations due to AEs were likewise doubled. However the effect of age >45 years on SAEs and discontinuations appears to also apply to the oral formulation.

## **First round benefit-risk assessment**

### **First round assessment of benefits**

The benefits of Abilify Maintena in the proposed usage are:

---

<sup>19</sup> Dose dumping was considered under PKs

Study 31-07-246 showed that time to impending relapse was significantly shorter for subjects on placebo compared with subjects on aripiprazole IM depot 400/300 mg in the double-blind, placebo-controlled Phase (p < 0.0001 log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole IM depot comparison was 5.029 (95% CI = 3.154, 8.018).

The provision of a depot formulation for those patients who respond to aripiprazole means:

- The possibility of better adherence/oversight of compliance compared to oral medication.
- A decreased demand on health care providers compared with administration of the IM regimen.

### **First round assessment of risks**

The risks of Abilify Maintena in the proposed usage are:

- An increased risk of suicidal ideation/suicide.
- The risk of injection site reactions.
- The lack of adequate data in the elderly.
- While oral formulation study in patients with severe renal impairment showed AUC was 15% lower for aripiprazole, C<sub>max</sub> was 36% higher, suggesting the possibility of mean sub-therapeutic levels towards the end of the cycle.
- Most of the existing risks associated with Abilify oral or IM formulations.

### **First round assessment of benefit-risk balance**

The benefit-risk balance of Abilify Maintena is unfavourable given the proposed usage but would become favourable if the changes recommended below are adopted.

### **First round recommendation regarding authorisation**

The sponsors proposes the indication:

*For the treatment of schizophrenia*

It is not recommended that the submitted proposed Indication be approved.

In both studies submitted (31-07-246 and 31-07-247) initial treatment with IM depot was associated with oral treatment for the first 14 days. The sponsors support for the use of a sole injection of 400 mg Abilify Maintena is based on a PopPK analysis with no clinical or PK/PD studies.

Analysis of a single 400mg IM depot dose is shown to achieve mean sub-therapeutic levels for the first and last 3 days of the initial treatment cycle, presumably extensive metabolisers will fare worse. (See Figure 2).

It is recommended that Abilify Maintena be approved for the added indication of:<sup>20</sup>

---

<sup>20</sup> It would be very rare to start a patient on a depot preparation, as for example, dose titration is not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn CPM/ERP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia.



*For the maintenance of clinical improvement in the treatment of schizophrenia*

## Clinical questions

All questions were in relation to the PI and Consumer Medicine Information (CMI) documents and are therefore beyond the scope of this AusPAR.

## Second round benefit-risk assessment

The benefit-risk assessment has not changed from that expressed in the first round assessment.

## Second round recommendation regarding authorisation

The recommendation was the same as in the First round assessment.

# V. Pharmacovigilance findings

## Risk management plan

The sponsor submitted a Risk Management Plan Aripiprazole EU-RMP version 8.3 dated 19 September 2013 (data lock point 1 April 2013) and Abilify Maintena Australian Specific Annex (ASA) version 1.0 dated 27 September 2013; ASA version 2.0 dated 21 January 2014 which was reviewed by the TGA's Office of Product Review (OPR).

## Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

**Table 7. Summary of safety concerns**

Important identified risks	<ul style="list-style-type: none"> <li>• EPS, including tardive dyskinesia</li> <li>• NMS</li> <li>• Leukopenia</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Seizures</li> <li>• Hyperglycemia/diabetes</li> <li>• Suicide-related events</li> <li>• Orthostatic hypotension</li> <li>• Dyslipidemia</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in pregnancy and lactation</li> <li>• Use in elderly patients &gt;65 years of age</li> </ul>

Notwithstanding the evaluation of the nonclinical and clinical aspects of the safety specifications (SS), it is noted that a list of identified safety concerns associated with aripiprazole oral and immediate release IM formulations are not included the above list for aripiprazole IM depot formulation as follows:

### **Potential risks:**

- Weight gain
- Somnolence/fatigue
- Cardiovascular-related disorders
- Conduction abnormalities



- Growth
- Low prolactin in paediatric patients
- Dysphagia
- ADHD<sup>21</sup> co-morbidity
- Drug interactions
- Increased mortality and CVA<sup>22</sup> in elderly patients with dementia
- Serious injection site reactions
- Serious hypersensitivity reactions
- Pathological gambling
- Serotonin syndrome
- Hepatic adverse events

***Missing information:***

- Use in paediatrics

***Recommendation 1.***

As these safety issues are not expected to be route of administration specific (except injection site reaction, which is a risk associated with injection formulation), the sponsor should include them in the safety concerns list for aripiprazole IM depot formulation or provide justification for not doing so. Other relevant parts of the EU-RMP and the ASA, including the pharmacovigilance plan and risk minimisation plan, should also be updated to ensure consistency.

***Sponsor's response***

The sponsor acknowledges that the listings of safety concerns in the EU-RMP for aripiprazole oral/immediate-release IM formulations (Abilify®) and aripiprazole IM depot formulation (Abilify Maintena®) differ. Please find a brief background and a justification of the variations below.

***RMP – Part II Safety specification***

A safety concern is defined as an important identified risk, important potential risk, or important missing information in the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems.<sup>1</sup>

Overall, the important identified risks and important potential risks in the safety specification of the EU-RMP, version 8.3, for Abilify and Abilify Maintena are aligned, with the exception of leukopenia, which the European Pharmacovigilance Risk Assessment Committee (PRAC) considered to be an important identified risk for Abilify Maintena based on potentially clinically significant (PCS) laboratory white blood cell count values from the pivotal trial, Trial 31-07-247. This risk only applies to Abilify Maintena, as leukopenia-related events are potentially more serious if they occur while on a depot formulation where action is not readily reversed.

Furthermore, with regards to missing information, there is a difference between Abilify and Abilify Maintena based on the clinical development program, indications and extent of postmarketing experience. For Abilify Maintena, 'Use in pregnancy and lactation' and 'Use

---

<sup>21</sup> ADHD=Attention Deficiency Hyperactivity Disorder

<sup>22</sup> CVA=cerebrovascular accident

in elderly patients > 65 years of age' are considered missing information as pregnant/lactating women and elderly subjects were not included in the clinical trials and the postmarketing safety experience in these populations is still very limited. For oral Abilify, 'Use in pregnancy and lactation' and 'Use in paediatrics' is considered missing information. 'Use in paediatrics' is not included as a safety concern for Abilify Maintena, as the depot formulation is not indicated for paediatric use and a Paediatric Investigation Plan (PIP) waiver has been granted by the EMA for this formulation.

As per RMP guidance, differences between indications, formulations, and target populations, if several medicinal products have the same active substance, will be accommodated by dividing the relevant parts of the RMP into modules and/or sections. This direction has been applied to the EU-RMP for aripiprazole to distinguish between Abilify and Abilify Maintena.

The safety specification of the RMP provides information on the important identified risks and important potential risks associated with use of the product. These should include only the important identified and important potential adverse events/reactions; the important identified and important potential interactions with other medicinal products, foods and other substances; and the important pharmacological class effects.

Nevertheless, despite the guidance only to include the important identified and important potential risks in the safety specification of the EU-RMP, a list of 'potential risks' has, with the acceptance of Pharmacovigilance Risk Assessment Committee (PRAC), remained in the Abilify section for historic reasons. The safety specification section for Abilify Maintena, which has also been endorsed by the PRAC, complies fully with the new EU PV legislation and guideline on GVP Module V Risk Management Systems.

The sponsor proposes to update the Australian Specific Annex section 3 to include a summary of both the safety specifications for Abilify and Abilify Maintena in order to provide full transparency and overview.

#### *RMP – Part III Pharmacovigilance plan*

Abilify and Abilify Maintena are both subject to routine pharmacovigilance activities. As part of the paediatric investigation plan (PIP), Abilify has two additional pharmacovigilance activities (Trials 31-09-266 and 31-09-267). These trials are designed to investigate safety and tolerability in the paediatric population. As a further additional pharmacovigilance activity, Abilify has a post-authorisation safety study (PASS, Trial 31-13-300), which assesses the effectiveness of the educational programme that is aimed to communicate and reinforce the safety messages when treating paediatric patients with bipolar disorder. Abilify Maintena is not indicated for paediatric use and a paediatric study plan PIP waiver has been granted by the EMA for this formulation, and hence these additional pharmacovigilance activities do not apply to Abilify Maintena.

In contrast, Abilify Maintena has two additional pharmacovigilance activities intended to investigate the EPS-related adverse events: a long-term safety trial (Trial 31-10-270) and a PASS (Trial 15893N). These activities were considered relevant for Abilify Maintena as the rate of EPS-related adverse events was higher than that in the oral Abilify group in the pivotal trials (18% versus 12%). However, when considering the historical oral aripiprazole data of EPS, the incidence of EPS related events for the oral formulation ranged from 8 to 32% (in the short-term studies) and from 17 to 27% (in the long-term studies). The low incidence (12%) of EPS-related adverse events observed in the patients treated with oral aripiprazole in the pivotal trial, Trial 31-07- 247, may consequently be explained by the design of this specific trial as the patients were stabilised on oral aripiprazole for a minimum of 8 weeks prior to randomisation, thereby lowering the incidence of EPS-related adverse events in this patient cohort.

### *RMP - Part V Risk minimisation measures*

According to the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems, for active substances for which there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product.

Both medicinal products are subject to routine risk minimisation measures, including approved PI and Consumer Medicine Information (CMI) and the legal status of prescription only medicine.

The risk minimisation measures in the EU-RMP for aripiprazole have been divided into separate sections for Abilify and Abilify Maintena as the risks differ according to the target population. The paediatric population, which is only applicable for Abilify, is considered particularly susceptible to certain safety concerns, hence the need for additional risk minimisation measures in order to safeguard this vulnerable population.

Abilify, due to its paediatric indication, has an additional risk minimisation measure in the form of educational material, which is provided to the prescribers to clearly highlight the need to carefully consider the indicated age range, dose, and duration of treatment before prescribing aripiprazole to a paediatric patient with bipolar I disorder, as well as patient brochures to help understand and be vigilant of specific adverse events. A PASS (Trial 31-13-300) has been proposed to assess the effectiveness of the educational programme.

Abilify Maintena does not have a paediatric indication and no additional risk minimisation measures have been proposed or requested by any regulatory authority.

### *Conclusion*

The sponsor does not consider the common EU-RMP for aripiprazole to be inconsistent with respect to pharmacovigilance activities and risk minimisation measures for Abilify or Abilify Maintena. Due to variations in the clinical development programs, indications, target populations, life-cycle stage, safety experience, and regulatory requests, the pharmacovigilance activities and risk minimisation measures differ in order to address the specific safety concerns effectively.

The sponsor considers the current EU-RMP applicable to the Australian setting and will include a summary of the safety specifications for both Abilify and Abilify Maintena in the Australian Specific Annex in order to provide full transparency and overview. Background and justification for the apparent differences in the EU-RMP between Abilify and Abilify Maintena, which are predominantly due to the paediatric indication for Abilify, have been provided above. For the EU-RMP, which only recently has been updated and approved by the EMA, no further updates to the safety specification, pharmacovigilance plan, or risk minimisation plan are deemed relevant at this point in time. However, the ASA will be updated as described above and further in the response to Recommendation 6.

### *OPR evaluator comment*

The sponsor's justification for not including 'use in paediatrics' as missing information in the RMP is acceptable. However, the evaluator considers the following potential risks are *'important potential adverse events/reactions; the important identified and important potential interactions with other medicinal products, foods and other substances; and the important pharmacological class effects'* that are associated with the active ingredient:

- Cardiovascular-related disorders
- Conduction abnormalities
- Increased prolactin level
- Dysphagia

- ADHD co-morbidity
- Drug interactions
- Increased mortality and CVA in elderly patients with dementia
- Serious injection site reactions
- Serious hypersensitivity reactions
- Pathological gambling
- Serotonin syndrome
- Hepatic adverse events

The OPR evaluator is aware that the EU-RMP submitted was prepared primarily for the EU regulators. Therefore, it is recommended that these risks be added as ongoing safety concerns in the Australian-specific Annex to the EU-RMP. The sponsor should undertake to give specific consideration of all reported occurrences of these adverse events in the Periodic Safety Update Reports.

### Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns (see Table 8) except for Extrapyramidal symptoms (EPS) including tardive dyskinesia for which additional pharmacovigilance is proposed as summarised in Table 8 below.

**Table 8. Summary of the proposed pharmacovigilance activities proposed in the EU-RMP and ASA for EPS and tardive dyskinesia**

Important identified risks	
Extrapyramidal symptoms (EPS) including tardive dyskinesia	<p>Routine Pharmacovigilance</p> <p>An Open-label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia (Study 31-10-270).<sup>23</sup></p> <p>A post-authorization safety study (PASS) will be conducted using automated databases to further assess the risk of EPS-related events.<sup>24</sup></p>

#### *Recommendation 2.*

The sponsor should provide an attachment to the ASA setting out the forthcoming studies and the anticipated dates for their submission in Australia.

#### *Sponsor's response*

The sponsor proposes to add Panel 1 to the ASA, as Appendix I, summarising the forthcoming studies and the anticipated dates for their submission in Australia.

<sup>23</sup> Study 31-10-270 is an ongoing open-label, multi-centre study extending the treatment of aripiprazole IM Depot to patients with schizophrenia who have completed the 52 week open-label safety and tolerability study 31-08-248. The planned completion date of the study is the end of 2018 with final study report expected in 2019. The sponsor has advised in the ASA that three Australian sites will recruit patients for this study

<sup>24</sup> A post-authorisation safety study (PASS) is a cohort study on EPS in patients treated with aripiprazole IM Depot with a two year follow-up using three databases from European countries (Sweden, Germany and Spain). It is planned to include 500 patients per database with study reports expected in 2019 to 2020. The sponsor has advised in the ASA that although this study does not involve Australian patients, the findings will be of value under Australian context.

*OPR evaluator comment*

The sponsor's response is satisfactory.

*Recommendation 3.*

It is noted that two studies, Studies 31-09-266 and 31-09-267 are being conducted to monitor hyperglycaemia, suicide related events, orthostatic hypotension, dyslipidemia and a few other safety concerns for aripiprazole oral and IM immediate-release formulations. There is no additional pharmacovigilance proposed for monitoring the same safety concerns for the IM depot formulation. The sponsor should provide justification as to why additional studies are not needed for the IM Depot formulation.

*Sponsor's response*

Trials 31-09-266 and 31-09-267 are briefly described below for convenience:

- Trial 31-09-266 is a long-term, multi-centre, randomised, double-blind, placebo-controlled trial conducted to evaluate the efficacy, safety, and tolerability of oral aripiprazole in adolescent patients (aged 13 to 17 years) with schizophrenia.
- Trial 31-09-267 is a long-term, multi-centre, open-label trial conducted to evaluate the safety and tolerability of flexible-dose oral aripiprazole in child or adolescent patients. Patients enrolled had either completed Trial 31-09-266 or were de novo patients with schizophrenia or bipolar I disorder, manic or mixed episode with or without psychotic features (aged 10 to 17 years).

Both these trials are being conducted in a paediatric population, and the sponsor acknowledges the importance of evaluating safety concerns, such as hyperglycaemia, suicide related events, orthostatic hypotension, and dyslipidaemia in this patient population.

Otsuka, as the marketing authorisation holder in the EU, has received a full waiver from the EMA for conducting trials for the treatment of schizophrenia in all paediatric and adolescent populations (from birth to less than 18 years of age) for Abilify Maintena on the grounds that the disorder does not occur in the paediatric subset (from birth to less than 13 years of age) and that Abilify Maintena does not represent a significant therapeutic benefit over existing treatments for adolescent subset (from 13 to less than 18 years of age). In addition, Otsuka has received a full waiver from the FDA for conducting trials for the treatment of schizophrenia in all paediatric and adolescent populations (from birth to less than 18 years of age) for Abilify Maintena.

In conclusion, the sponsor does not consider it applicable to conduct additional trials in the child and adolescent populations as no paediatric indication is being sought for Abilify Maintena and, in addition, waivers have been granted from both the EMA and the FDA to investigate Abilify Maintena in this population.

*OPR evaluator comment*

The sponsor's response is satisfactory.

*Recommendation 4.*

Pending approval of the product, the sponsor should undertake to communicate findings from the studies to the TGA in the PSURs in the same time frame as they are communicated to other regulatory agencies.

*Sponsor's response*

In the EU, Periodic Benefit-Risk Evaluation Reports (PBRERs) for aripiprazole are required to be submitted at 1 year intervals, with a data-lock point 16 July 20xx, and deadline for submission 24 September 20xx. The PBRER replaces the PSUR in accordance with the new EU pharmacovigilance legislation.<sup>25</sup>

The sponsor proposes to follow the same submission cycle for PBRERs in Australia as that agreed with the EU, except the deadline for submission will be within 90 days after the datalock point (that is, by 14 October 20xx).

It is proposed that PBRERs be submitted covering a minimum of 3 years after approval in Australia. The first PBRER to be submitted will be the first one with a data-lock after approval of Abilify Maintena in Australia (thus, this is currently expected to be the PBRER issued in 2015).

*OPR evaluator comment*

The sponsor's response is satisfactory.

*Recommendation 5.*

As PASS will be dependent on post authorisation data in EU countries, the sponsor should clarify what it plans to do in case its applications to overseas regulatory agencies in the EU are rejected or deferred.

*Sponsor's response*

In the EU, marketing authorisation was granted on 15 November 2013 via the EU Centralised Procedure. As agreement on the outline of the PASS (Trial 15893N) was part of the approval, a rejection or deferral is not an option. The final protocol was submitted to the EMA on 18 November 2013. The final report is expected to be submitted to the TGA in third quarter of 2020.

*OPR evaluator comment*

The sponsor's response is satisfactory.

**Risk minimisation activities**

The sponsor states:

*'No additional risk minimisation measures are warranted at this time. Routine pharmacovigilance practice and appropriate prescribing information in the PI (routine risk minimisation) are considered sufficient. A copy of the proposed PI was submitted with the initial application in Module 1 (27 May 2013).*

*The PI will be provided as a package insert in the convenience kit pack. A Quick Reference Guide containing instructions on how to administer the injection and manufacturer's instructions for using the safety needle will also be included in the pack. The reconstitution and administration of ABILIFY MAINTENA by a healthcare professional will ameliorate any potential risks associated with the injection procedure.'*

The sponsor's approach and justification appear to be reasonable and therefore satisfactory.

*Recommendation 6.*

The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in

---

<sup>25</sup> Regulation [EU] No. 1235/2010 and Directive 2010/84/EU

the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.

*Sponsor's response*

As requested, the sponsor will include or refer to tables summarising the safety specification, the pharmacovigilance plan, and the planned risk minimisation measures in the Australian context to sections 2 and 3 of the ASA. Panel 2 summarises the safety concerns for Abilify Maintena (the information has not been modified from that provided in the EU-RMP, as the same safety concerns are also applicable to Australia). The sponsor will include a cross-reference in the ASA to the EU-RMP, version 8.3, which summarises the planned pharmacovigilance actions for Abilify Maintena (the information has not been modified from that provided in the EU-RMP, as the same pharmacovigilance activities are also applicable to Australia). Panel 4 summarises the routine risk minimisation measures for Abilify Maintena in the EU and Australia, and has been modified to include routine risk minimisation measures in the proposed Australian PI and CMI, as requested.

*OPR evaluator comment*

The sponsor's response is satisfactory.

*Recommendation 7.*

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows:

- The PI should provide clearer guidance on switching from aripiprazole IM Depot to other antipsychotic treatment to include information on when oral or other type of treatment should be restarted if required. This is to ensure therapeutic effects are maintained and the chance of side effects are minimised;
- 'Step 4: Injection Procedure' in the PI be modified to stress the importance of examining depth of subcutaneous fat at the injection site and choosing the appropriate needle size to ensure adequate drug delivery.

*Sponsor's response*

*Guidance on switching medication*

Switching from Abilify Maintena to other antipsychotic treatment has not been systematically studied in the clinical trials. In general, when switching a patient from a depot formulation to other antipsychotic treatment, the depot formulation should be ceased and the new treatment gradually up-titrated. However, the recommended initiation schedule varies between different products and needs to be adjusted based on the individual patient's clinical status. In the current PI, the sponsor has already included guidance on discontinuation of Abilify Maintena, however, the sponsor proposes to include a subheading for this to make it more visible to the treating physicians:

*'Discontinuation of ABILIFY MAINTENA*

If ABILIFY MAINTENA is discontinued, its prolonged-release characteristics must be considered.'

This will be updated with the PI included in the pre-ACPM response.

The guidance provided is in line with the PI for Invega Sustenna and Risperdal Consta.

*Injection procedure*

The sponsor proposes to add the following additional guidance to the PI (underlined text) to stress the importance of examining depth of subcutaneous fat at the injection site and choosing the appropriate needle size to ensure adequate drug delivery:

*'b) Select one of the following Hypodermic Needle-Pro™ needles and attach the needle to the BD Luer-Lok™ syringe containing the suspension for injection. To avoid subcutaneous drug administration, examine the depth of subcutaneous fat at the injection site and select the appropriate needle size. Ensure the needle is firmly seated on the Needle-Pro™ safety device with a push and clockwise twist and then pull the needle cap straight away from the needle (see Diagram 10).'*

## **Summary of recommendations**

### ***Outstanding issues***

Details of the following outstanding issue are discussed above.

#### ***Recommendation 1***

The sponsor's justification for not including 'use in paediatrics' as missing information in the RMP is acceptable. However, the evaluator considers the following potential risks are *'important potential adverse events/reactions; the important identified and important potential interactions with other medicinal products, foods and other substances; and the important pharmacological class effects'* that are associated with the active ingredient:

- Cardiovascular-related disorders
- Conduction abnormalities
- Increased prolactin level
- Dysphagia
- ADHD co-morbidity
- Drug interactions
- Increased mortality and CVA in elderly patients with dementia
- Serious injection site reactions
- Serious hypersensitivity reactions
- Pathological gambling
- Serotonin syndrome
- Hepatic adverse events

The OPR evaluator is aware that the EU-RMP submitted was prepared primarily for the EU regulators. Therefore, it is recommended that these risks be added as ongoing safety concerns in the ASA to the EU-RMP. The sponsor should undertake to give specific consideration of all reported occurrences of these adverse events in the Periodic Safety update Reports.

### ***Advice from the Advisory Committee on the Safety of Medicines (ACSOM)***

ACSOM advice was not sought for this submission.

### ***Comments on the safety specification of the RMP***

#### ***Clinical evaluation report***

The OPR evaluator supports the comments made by the clinical evaluator. The risk of suicide related events and use in elderly have been included as ongoing safety concerns in the RMP. The evaluator has recommended that the risk of serious injection site reactions be added as an ongoing safety concern in the ASA and managed through adequate reporting.



### *Nonclinical evaluation report*

The OPR evaluator supports the comments made by the nonclinical evaluator. Detailed recommendations regarding the Product Information were provided in the nonclinical evaluation report but these are beyond the scope of this AusPAR.

### ***Suggested wording for conditions of registration***

#### ***RMP***

Implement RMP Aripiprazole EU-RMP version 8.3 dated 19 September 2013 (data lock point 1 April 2013) with Australian-specific Annex version 2.0 dated 21 January 2014 and any future updates as a condition of registration.

## **VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

The clinical evaluator stated that the proposed dose of 400 mg monthly (no sooner than 26 days after the previous injection) compares with that calculated for 26 days (253.5 mg at the recommended dose of 9.75 mg/day or 780 mg at the maximum dose of 30 mg/day) of the standard IM Abilify treatment (already registered with a different indication *agitation associated with schizophrenia*) and oral Abilify treatment of schizophrenia and bipolar I disorder (260 to 390 mg per 26 days at 10 to 15 mg/day or maximum 780 mg for 26 days at 30 mg/day). The absolute oral bioavailability of the tablet Abilify formulation is 87%.

### **Quality**

The application for registration of the IM depot injection kit included results from a Phase II study that established to the TGA's satisfaction that absorption of aripiprazole from the IM depot formulation was complete relative to an IM standard formulation based on dose adjusted  $AUC_{(0-t)}$  values and the maximum cumulative fraction of dose absorbed as determined by deconvolution analysis (see *Quality Findings* above).

There were no objections to registration from a quality and biopharmaceutical perspective.

### **Nonclinical**

There were no major deficiencies in the nonclinical dossier.

The new primary pharmacology data were consistent with previous studies attributing the antipsychotic activity to actions at various receptor subtypes. Safety pharmacology data on aripiprazole were adequately evaluated previously. No additional pharmacology data specifically using the IM depot formulation are necessary.

The pharmacokinetic studies indicate that absorption of aripiprazole is slow and prolonged following administration of the IM depot formulation, with a  $T_{max}$  of 168 h in rats and a long plasma half-life. In repeat dose studies, absorption was dose proportional and similar for both sexes. There was high retention of aripiprazole in the injection site muscle following administration of IM depot formulation. By contrast, aripiprazole was rapidly absorbed and showed wide tissue distribution following administration of IM aqueous formulation. The major substance at the injection site and in plasma was unchanged aripiprazole, with no evidence of the formation of new metabolites at the injection site following administration of the IM depot formulation. In mini-pigs, the AUC

ratio of the pharmacologically-active metabolite dehydro-aripiprazole (OPC-14857) to aripiprazole was similar following administration by IV, IM and SC routes. Excretion following IM depot formulation was not examined but following IM aqueous formulation, faeces was the major excretion route (92%), as it was following oral administration.

Repeat dose and local tolerance studies with the IM depot formulation reported inflammatory effects at the injection site, with some evidence of posttreatment recovery. The known systemic effects of aripiprazole were also confirmed.

There are no changes to the previously documented genotoxicity and carcinogenicity profiles and no additional genotoxicity or carcinogenicity data specifically using the IM depot formulation are necessary.

The reproductive and developmental toxicity of aripiprazole was adequately evaluated previously. Given the lower exposure from the IM depot formulation, no additional studies using the IM depot formulation are necessary. Pregnancy Category C is appropriate.

Based on the nonclinical data evaluated herein, there are no nonclinical objections to the registration of aripiprazole IM depot formulation as proposed.

Amendments to the draft Product Information document were also recommended.

## **Clinical**

The clinical evaluator (CE) identified nine studies with PK data, two pivotal efficacy and safety studies, five other efficacy and safety studies and one PSUR. See *Clinical Findings above*, in particular evaluator's conclusions on pharmacokinetics, Efficacy and Safety as well as Attachment 2 Extract from the CER for further details on the clinical evaluation.

The CE recommended that Abilify Maintena be approved for an amended indication of:

*For the maintenance of clinical improvement in the treatment of schizophrenia.*

See discussion below.

## **Risk management plan**

*See Pharmacovigilance findings above.*

## **Risk-benefit analysis**

### **Delegate's discussion and considerations**

It is acknowledged that all the evaluators have raised no objection (even though the clinical evaluator has queried the efficacy outcome for Study 31-07-247, due to the fact that its analytical method was changed midway through the course of the study) to the registration of the new dosage form and strengths of aripiprazole (Abilify Maintena).

While the clinical evaluator is of the opinion that a rejection of the efficacy outcome analysis from Study 31-07-247 is the only option available based on its flawed methodology, the Delegate believes that there is a trend, when everything is taken together, towards the efficacy of Abilify Maintena in this submission. In that regard, the approval/registration of the other dosage forms of aripiprazole for schizophrenia/other indications had been previously stated. Additionally, the clinical evaluator has rationally proposed modification to the sponsor's submitted indication from

*For the treatment of schizophrenia*

to

***For the maintenance of clinical improvement in the treatment of schizophrenia.***

The clinical evaluator's rationale is restated below:

*"It would be very rare to start a patient on a depot preparation, as e.g. dose titration is not possible, an acute effect may be needed or undesirable effects may occur, in which case the preparation cannot be withdrawn CPMP/EWP/49/01 Appendix to the Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia - Methodology of Clinical Trials Concerning the Development of Depot Preparations of Approved Medicinal Products in Schizophrenia."*

While in unison with the clinical evaluator to modify the sponsor's submitted indication, the Delegate proposes a minor adjustment as follows:

*For the maintenance treatment of schizophrenia where clinically appropriate.*

Apart from the clinical evaluator's comment on the issue, Studies 31-07-246 and 31-07-247 were titled as maintenance treatment investigations of Abilify Maintena and eligibility into their randomised Abilify Maintena phase requires prior oral conversion phase followed by oral stabilisation phase; meaning that treatment was not initiated with Abilify Maintena but rather maintained by it. Also eligible, were patients with relapse history due to not taking their antipsychotics, hence the tag "clinically appropriate" to the modified indication.

There are no major concerns in terms of safety and the benefit-risk balance is regarded favourable provided the proposed modified indication is accepted.

The draft PI requires amendments as suggested in the clinical (except for the indication), nonclinical and RMP evaluation reports before finalisation of the application.

***Summary of issues***

- The interim analysis stopping rules were applied for Study 31-07-246 (a 52 week, multi-centre, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of an Intramuscular depot formulation of aripiprazole as maintenance treatment in patients with schizophrenia "ASPIRE US") after 50% of impending relapse events (64) had occurred with the trial being terminated thereafter for ethical issues. Analysis of the primary efficacy outcome showed that time to impending relapse was significantly shorter for subjects on placebo compared to aripiprazole IM depot ( $p < 0.0001$ ; log-rank test).
- Almost 3 years after the start of the trial (14 July 2011), the primary efficacy endpoint for Study 31-07-247 (A 38 week, multi-centre, randomized, double-blind, active-controlled study to evaluate the efficacy, safety, and tolerability of an intramuscular depot formulation of aripiprazole as maintenance treatment in patients with schizophrenia "ASPIRE EU") was changed to '*time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 3*' to '*the proportion of subjects experiencing exacerbation of psychotic symptoms/impending relapse by end of 26 weeks of treatment from the date of randomization in Phase 3, in schizophrenic subjects who have maintained stability on oral aripiprazole for at least 8 consecutive weeks in Phase 2 of the study.*' The primary efficacy outcome as per the **changed** endpoint was that the estimated proportion of subjects experiencing impending relapse by end of Week 26 was 7.12% in the aripiprazole IM depot 400/300mg group and 7.76% in the oral aripiprazole tablets 10 to 30mg group, a difference of -0.64%. The 95% CI (-5.26, 3.99) for the difference in the estimated proportion of subjects experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5%. Based on that, aripiprazole IM depot 400/300 mg is non-inferior to the aripiprazole oral tablets 10 to 30 mg formulation. If the original primary endpoint was used, that is, time to impending relapse, it would have been required first to show

statistical superiority of IM depot 400/300 mg over IM depot 50/25 mg group (HR.317 95%CI 0.182, 0.552;  $p < 0.0001$ ) followed by testing non-inferiority of IM depot 400/300 mg to oral tablets 10 to 30 mg using a 95% (two sided) CI for the HR (aripiprazole IM depot 400 or 300 mg versus oral aripiprazole). Then, if the upper bound of the HR CI was lower than 1.68, a non-inferiority of aripiprazole IM depot (400 or 300 mg) to oral aripiprazole could be declared. The upper bound for the *original primary objective endpoint* however, did exceed 1.68 (0.991, 95% CI 0.545, 1.803;  $p = 0.9920$ ). However, while the clinical evaluator is of the opinion that a rejection of the efficacy outcome analysis from Study 31-07-247 is the only option available based on its flawed methodology, the Delegate believes that there is a trend, when everything is taken together, towards the efficacy of Abilify Maintena in this submission.

- The sponsor's proposed indication does not match the design of efficacy/safety Studies 31-07-246 and 31-07-247 and the issue has been commented upon by both the clinical evaluator and Delegate with suggested modification.

### **Delegate's proposed action**

The Delegate had no reason to say, at this time, that the application to register new dosage form and dosage strengths of aripiprazole (Abilify) should not be approved subject to resolving issues, arising from the Advisory Committee on Prescription Medicines (ACPM) deliberations and finalisation of matters pertaining to the draft PI and RMP to the satisfaction of the TGA.

### **Delegate's request for ACPM advice**

The following questions were posed to the ACPM:

1. Overall acceptability or otherwise of the submitted and already evaluated efficacy/safety data package.
2. Acceptability or otherwise of the Delegate's modified indication for approval.
3. The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

#### ***Proposed changes to the indication***

The sponsor agrees with the Delegate's and clinical evaluator's proposal to include 'maintenance' in the indication, however, the sponsor proposes not to include '*where clinically appropriate*': '*For maintenance treatment of schizophrenia*'. In regulatory and medical contexts, specifying '*where clinically appropriate*' in the indication is normally linked to a special situation. The overall benefit-risk evaluation of the submitted dossier for Abilify Maintena supports the use in maintenance treatment of schizophrenia.

There is no additional specific clinical circumstance (such as Safety, use in a subset of patients) that requires the inclusion of the phrase '*where clinically appropriate*', therefore it is the sponsor's view that this phrase is not required.

All drugs approved should only be used when clinically appropriate in the approved target population and as instructed in the label. Adding '*where clinically appropriate*' would indicate a concern with the use of Abilify Maintena, which is not the case. Therefore, it is the sponsor's view that this phrase is not required, and furthermore it is not included in the recently approved indications for Invega Sustenna and Saphris.

***Issue raised in delegate's request for ACPM advice******Advice sought by delegate***

*Overall acceptability or otherwise of the submitted and already evaluated efficacy/safety data package.*

***Summary applicant's response***

Overall, the Delegate and the evaluators believe that the dossier for Abilify Maintena is approvable. However, concerns were expressed with the study methodology for Trial 31-07-247. The following points summarise the sponsor's response to this issue; more detailed responses follow:

- *Validity of the methodology for Trial 31-07-247*
- *Clinical value of Trial 31-07-247 to the prescriber*
- *Update on publication of Trial 31-07-247*
- *Regulatory approvals in the EU, Canada, Switzerland and the US<sup>26</sup>*

The sponsor reiterates that no interim analysis was performed for Trial 31-07-247, although this was asserted by the evaluator in the Clinical Evaluation Report. This has already been stated in our previous response to the Clinical Evaluation Report. The changes to the protocol of Trial 31-07-247 were made based on a review of blinded data and after consultation with the European Medicines Agency (EMA). In addition, these changes are in accordance with the ICH *Statistical Principles for Clinical Trials*.<sup>27</sup> The EMA acknowledged that the change of the primary endpoint could be made without impacting the type 1 error, since no interim analysis had been planned or performed. The primary objective of the study did not change; rather it was the primary endpoint and corresponding non-inferiority margin that addressed the primary objective that were changed.

The sponsor holds the firm position that Trial 31-07-247 is a methodologically sound and clinically informative study, which should be considered a valid confirmatory study for the safety and efficacy of Abilify Maintena. Therefore, this trial merits inclusion in the *Clinical Trials* section of the *Product Information* for Abilify Maintena.

***Detailed response***

The sponsor would like to highlight that overall the Delegate and the evaluators find the dossier for Abilify Maintena approvable. However, they have expressed concerns with the study methodology for Trial 31-07-247, which effectively excludes it from the Product Information for Abilify Maintena. The sponsor would like to address and dispel the concerns raised regarding the methodology of Trial 31-07-247 in this Pre-ACPM Response.

All analyses were performed according to regulatory guidelines and no interim analysis was performed, although this was asserted by the clinical evaluator.

- *Validity of the methodology for Trial 31-07-247*

Trial 31-07-247 was a 38 week, multi-centre, randomised, double-blind, active-controlled study to evaluate the efficacy, safety, and tolerability of an intramuscular depot formulation of aripiprazole (Abilify Maintena) as maintenance treatment in patients with schizophrenia. The trial consisted of a screening phase and three treatment phases: a conversion phase, an oral stabilisation phase, and a double-blind, active-controlled phase.

<sup>26</sup> This part of the response has been inserted at *Regulatory status* at the beginning of this AusPAR.

<sup>27</sup> ICH Harmonised Tripartite Guideline E9: Statistical Principles for Clinical Trials. CPMP/ICH/363/96. 1998. Adopted by the TGA 1 October 1999.

The primary objective of the trial was to demonstrate non-inferiority of Abilify Maintena 400 mg/300 mg to oral aripiprazole tablets 10 to 30 mg in subjects who had maintained stability on oral aripiprazole for at least 8 consecutive weeks during the oral stabilisation phase.

In the Delegate's Request for ACPM's Advice concern was expressed regarding the methodology used for Trial 31-07-247, which is in accordance with the clinical evaluator's conclusion.

The sponsor disagrees with the Delegate's and clinical evaluator's conclusions regarding this trial and has provided arguments below to show that Trial 31-07-247 is methodologically sound and should be regarded as part of the confirmatory evidence for the efficacy of Abilify Maintena 400 mg and 300 mg.

Trial 31-07-247 was designed with the primary objective of showing non-inferiority of Abilify Maintena (400 mg/300 mg) to oral aripiprazole tablets 10-30 mg based on the primary endpoint: time to exacerbation of psychotic symptoms/impending relapse. The non-inferiority margin was stated as a hazard ratio of 1.68. The original protocol explains how this corresponds to a non-inferiority margin of 15%, with an assumed 30% proportion of patients on oral aripiprazole experiencing exacerbation of psychotic symptoms/impending relapse.

While no interim analysis (with subsequent un-blinding of data) was planned or performed for this trial, although this was asserted by the clinical evaluator, a blinded data review meeting was held on 1 October 2010, in alignment with the ICH Statistical Principles for Clinical Trials.<sup>27</sup> At the meeting, it became apparent that the overall impending relapse rate was substantially lower than the one projected in the protocol. A total of 117 patients had completed the randomised, double-blind, active-controlled phase of the trial; however, only 36 impending relapses had been observed. According to the trial protocol, 275 impending relapses were required for the testing of the primary endpoint. Due to the lower than anticipated impending relapse rate, the power of the originally planned analysis was seriously deflated as this was driven by the number of events in a time-to-event analysis. Consequently, the EMA was consulted via a Scientific Advice. After the consultation, the trial sponsor amended the protocol by changing the primary endpoint to the estimated proportion of patients experiencing impending relapse.

The EMA acknowledged that the change of the primary endpoint could be made without impacting the type 1 error since no interim analysis had been planned or conducted. The approach taken is in compliance with the ICH Statistical Principles for Clinical Trials<sup>27</sup>, where it is described how changes to the principal features of an analysis can be made prior to un-blinding, and the results from such an updated analysis can be regarded as confirmatory.

As described in the submission at (sponsor's) Summary of Clinical Efficacy, the change in the primary endpoint was implemented with Protocol Amendment 3, dated 14 July 2011; the oral aripiprazole relapse rate was assumed to be 18% and the non-inferiority margin was changed to 11.5%. It is acknowledged that this could imply a change in the primary objective, as the primary endpoint was mentioned in the primary objective in the protocol, however, this was not the case. The clinical objective of showing non-inferiority with respect to prevention of relapse, however, is equally well addressed by the revised primary endpoint, namely, the proportion of patients relapsing. Thus, the primary objective of the study did not change rather it was the primary endpoint and corresponding non-inferiority margin that addressed the primary objective that were changed. Furthermore, the amended endpoint is in accordance with the EMA *Appendix to the note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia – Methodology of clinical trials concerning the development of depot preparations of approved medicinal product in schizophrenia* (adopted by the TGA), as well

as the current EMA *Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia* (proposed for adoption by the TGA).<sup>28,29</sup>

The primary efficacy endpoint in the original protocol, time to exacerbation of psychotic symptoms/impending relapse, was included as a secondary endpoint in the protocol amendment. Furthermore, the sample size was revised from n=575 to n=650 patients, taking into account recommendations by the EMA that demonstration of assay sensitivity may require an increase in sample size, as low dose aripiprazole IM depot 50/25 mg (the pseudo-placebo arm) may be effective in preventing relapse in at least some part of the patient population.

The results of Trial 31-07-247 proved that Abilify Maintena was non-inferior to oral aripiprazole; the proportion of subjects experiencing impending relapse was 7.12% for Abilify Maintena 400/300 mg, 7.76% for oral aripiprazole 10-30 mg and 21.80% for the pseudoplacebo.

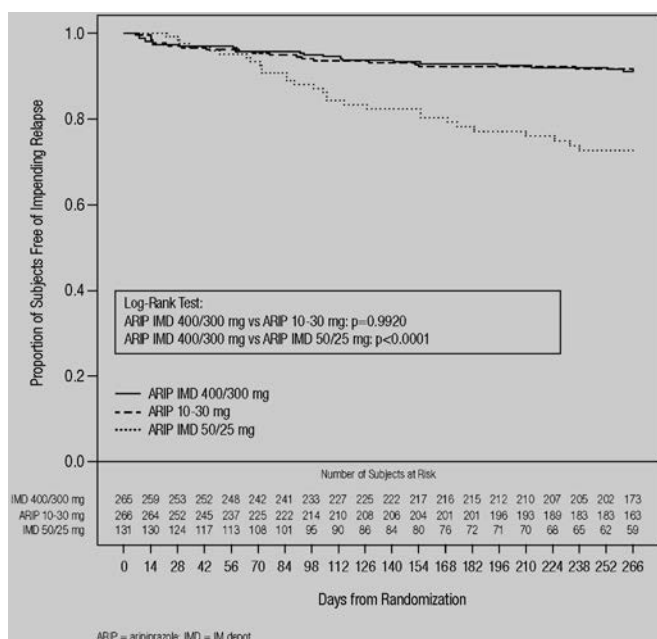
The upper 95% CI limit of the difference between the relapse rates for Abilify Maintena 400/300 mg and oral aripiprazole 10-30 mg was 3.99%, which was well below the pre-defined non-inferiority margin of 11.5%. Internal validity of Trial 31-07-247 was also demonstrated, as the effect of Abilify Maintena 400/300 mg clearly and significantly outperformed the pseudo-placebo, with an estimated difference in relapse rate of 14.68% (95% CI: -23.09%; -6.27%, p=0.0006). Furthermore, assay sensitivity of the Trial 31-07-247 is evident by the fact that the difference (-14.04%) between the oral aripiprazole 10-30 mg arm and the pseudo-placebo arm in the proportion of subjects experiencing impending relapse was statistically significantly in favour of oral aripiprazole 10 to 30 mg (95% CI: -22.53%; -5.56%, p = 0.001). These results are further supported by the Kaplan-Meier plot for time to impending relapse, where the curves for Abilify Maintena 400/300 mg and oral aripiprazole 10 to 30 mg are practically identical and clearly separated from the curve for the pseudo-placebo (see Figure 4).

---

<sup>28</sup> European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia. EMA/CHMP/40072/ 2010 Rev. 1. 2012. Proposed for adoption by the TGA 15 April 2014.

<sup>29</sup> European Medicines Agency (EMA). Committee for Proprietary Medicinal Products (CPMP). Appendix to the note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia - Methodology of clinical trials concerning the development of depot preparations of approved medicinal product in schizophrenia CPMP/EWP/49/01. 2003. Adopted by the TGA 17 September 2004.



**Figure 4. Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Double-blind, Active-controlled Phase Efficacy Sample)**

- *Clinical value of trial 31-07-247 to the prescriber*

It is the sponsor's strong opinion that Trial 31-07-247 provides important efficacy as well as safety information on Abilify Maintena to the prescribing physician. In particular, Trial 31-07-247 provides a direct comparison of Abilify Maintena 400 mg/300 mg to oral aripiprazole tablets 10 to 30 mg, which enables the prescriber to compare the efficacy and safety profile of Abilify Maintena with a well-established product. The comparable efficacy of Abilify Maintena and oral aripiprazole tablets is summarised in Table 9, which presents the mean change from baseline to Week 38 in PANSS total score.

**Table 9. PANSS Total Score – Change From Baseline to Week 38 – LOCF: Randomised Efficacy Sample a,b**

	<b>Abilify Maintena (n = 263)</b>	<b>Oral aripiprazole 10-30 mg/day (n = 266)</b>	<b>Aripiprazole Long- Acting Injectable 50 mg/25 mg (n = 131)</b>
<b>Mean baseline (SD)</b>	57.9 (12.94)	56.6 (12.65)	56.1 (12.59)
<b>Mean change (SD)</b>	-1.8 (10.49)	0.7 (11.60)	3.2 (14.45)
<b>P-value</b>	-	0.0272	0.0002

SD = standard deviation

<sup>a</sup> Negative change in score indicates improvement.

<sup>b</sup> Only patients having both baseline and at least one post baseline value were included. P-values were derived from comparison for change from baseline within analysis of covariance model with treatment as term and baseline as covariate.

Furthermore, the design of Trial 31-07-247, in which patients were stabilised on oral aripiprazole prior to randomisation to double-blind treatment with Abilify Maintena, reflects the intended use of Abilify Maintena in clinical practice. Thus, this trial provides the prescribing physician with an important and unbiased (double-blind) assessment of the efficacy of Abilify Maintena when switching from oral aripiprazole.

The primary endpoint in Trial 31-07-247 was the estimated proportion of patients experiencing an impending relapse, comparing Abilify Maintena to oral aripiprazole tablets, whereas the primary endpoint in Trial 31-07-246 was the time to impending relapse, comparing Abilify Maintena to placebo. While the primary endpoints in the two



trials are different, each of them provides clinically meaningful information to the prescriber, and should be seen as complementary.

- *Update on Publication of Trial 31-07-247*

A primary manuscript for Trial 31-07-247 describing the efficacy, safety, and tolerability of Abilify Maintena 400 mg/300 mg (Aripiprazole once-monthly for treatment of schizophrenia: a double-blind, randomized, non-inferiority study by Fleischhacker et al.) has been peer reviewed and accepted for publication in the British Journal of Psychiatry on 27 February 2014 (the letter of acceptance is available upon request). The manuscript is expected to be available online in June 2014.

### **Conclusion**

- In the regulatory and medical contexts, normally a specification in the indication of the use of a drug 'where clinically relevant' is linked to a special situation. Abilify Maintena is proposed to be indicated for maintenance treatment of schizophrenia. There is no additional specific clinical circumstance (for example, safety, use in a subset of patients) that requires the inclusion of the phrase, 'where clinically appropriate'. Therefore, it is the sponsor's view that this phrase is not required.
- The sponsor has the firm position that Trial 31-07-247 is a methodologically sound and clinically informative study, which should be considered a valid confirmatory study for the safety and efficacy of Abilify Maintena.
- No interim analysis was performed for Trial 31-07-247 although this was asserted by the evaluator in the *Clinical Evaluation Report*. Prior to any amendment of the protocol, the EMA acknowledged via a Scientific Advice that the change of the primary endpoint could be made without impacting the type 1 error, since no interim analysis had been planned or performed.
- The primary objective of the study did not change; rather, it was the primary endpoint and corresponding non-inferiority margin that addressed the primary objective that were changed. The amendment to the protocol of Trial 31-07-247 was made based on a review of blinded data, which is in accordance with the ICH *Statistical Principles for Clinical Trials*.
- Trial 31-07-247 provides the prescribing physician with a direct comparison of Abilify Maintena to oral aripiprazole 10 to 30 mg (a well-established product). Furthermore, the design of Trial 31-07-247 reflects the intended use of Abilify Maintena in clinical practice, and provides the prescribing physician with an important and unbiased (double-blind) assessment of the efficacy of Abilify Maintena when switching from oral aripiprazole. This additional information will not be readily available if Trial 31-07-247 is excluded from the Product Information.
- Abilify Maintena has been approved in the EU, Canada, and Switzerland, where both Trials 31-07-246 and 31-07-247 were included by the regulatory authorities in the approved labels for those markets. US approval was based on Trial 31-07-246 only, as
- Trial 31-07-247 was ongoing at the time of submission and was not required by the FDA.
- With all the above taken into account, the sponsor proposes that Trial 31-07-247 be retained as a key confirmatory study for safety and efficacy, which therefore merits its inclusion in the *Clinical Trials* section of the *Product Information* for Abilify Maintena.

**Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a major variation (strength) for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Abilify Maintena injection containing 300 mg or 400 mg of aripiprazole to have an overall positive benefit-risk profile for a variation to the proposed indication;

*For the maintenance of clinical improvement in the treatment of schizophrenia*

**Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following;

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA, specifically including the indication statement.

**Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:**

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

**Specific advice**

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- *Overall acceptability or otherwise of the submitted and already evaluated efficacy/safety data package*

The ACPM agreed with the Delegate that efficacy has been sufficiently demonstrated despite significant methodological problems being identified and that the safety profile is manageable. The ACPM observed that changing the primary efficacy endpoint for a study (Study31-07-247), 3 years after it started, was unusual and noted from the sponsor's pre-ACPM response that Study31-07-247 was neither required nor included in the Clinical Studies section of the US Prescribing Information (approved February2013) as per the sponsor's Pre-ACPM response.

- *Acceptability or otherwise of the Delegate's modified indication for approval*

The ACPM advised that a variation of the sponsor's proposed indication along the lines of *for the maintenance of clinical improvement in the treatment of schizophrenia* was a more accurate statement of the intended use of aripiprazole. In line with the clinical trial, patients should show improvement on oral treatment before switching to the injectable formulation.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, the TGA approved the registration of Abilify Maintena, aripiprazole (as monohydrate) 300 mg powder and solvent for prolonged release suspension for injection vial; and Abilify Maintena, aripiprazole (as

monohydrate) 400 mg powder and solvent for prolonged release suspension for injection vial:

*For maintenance of clinical improvement in the treatment of schizophrenia.*

**Specific conditions of registration applying to these goods**

1. The implementation of RMP Aripiprazole EU-RMP version 8.3 dated 19 September 2013 (data lock point April 2013) included with submission number 2013-01100-1-1 and any subsequent revisions as agreed with the TGA.

**Attachment 1. Product Information**

The Product Information approved for main Abilify Maintena at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/product-information-pi>>.

**Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>