CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cardioral 75 mg capsules, soft
IBSA Farmaceutici Italia S.r.L, Italy

acetylsalicylic acid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1385/001/DC
Registration number in the Netherlands: RVG 102708

21 July 2010

Pharmacotherapeutic group:	antithrombotic agents, platelet aggregation inhibitors excl. heparin
ATC code:	B01AC06
Route of administration:	oral
Therapeutic indication:	secondary prevention of myocardial infarction; prevention of cardiovascular morbidity in patients suffering from stable angina pectoris; history of unstable angina pectoris, except during the acute phase; prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG); coronary angioplasty, except during the acute phase; secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.
Prescription status:	prescription only
Date of authorisation in NL:	24 February 2010
Concerned Member States:	Decentralised procedure with CZ, EL, ES, FR, HU, IT, LU, PT, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Cardioral 75 mg capsules, soft, from IBSA Farmaceutici Italia S.r.L. The date of authorisation was on 24 February 2010 in the Netherlands.

The product is indicated for:

- secondary prevention of myocardial infarction.
- prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
- history of unstable angina pectoris, *except during the acute phase.*
- prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
- coronary angioplasty, *except during the acute phase*.
- secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.

Cardioral is not recommended in emergency situations. It is restricted to secondary prevention with chronic treatment.
A comprehensive description of the indications and posology is given in the SPC.

Acetylsalicylic acid, the prototype of salicylates, is a non-steroidal antiinflammatory drug (NSAID) with antiinflammatory, analgesic, antipyretic properties, which has antithrombotic activity at doses ranging from 20 to 325 mg. Acetylsalicylic acid irreversibly acetylates cyclooxygenase 1 (COX-1), this action being at the origin of its whole properties. At the platelets level, this inhibition blocks the thromboxane (Tx)-A2 synthesis and therefore inhibits platelet aggregation.
The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%.
Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.
Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cardegic 75 mg, powder for oral solution (NL license RVG 23207) which was first registered in the Netherlands by Sanofi Aventis B.V. on 11 October 1999. Cardegic 75 mg was withdrawn in the Netherlands for commercial reasons on 30 August 2007. In addition, reference is made to Cardegic authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 75 mg soft capsules is compared with the pharmacokinetic profile of the reference product Kardegic 75 mg powder for oral solution, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is acetylsalicylic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white, crystalline powder or colourless crystals. Acetylsalicylic acid is slightly soluble in water and freely soluble in ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and CEP, with no additional requirements. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The re-test period for the active substance is three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Cardioral 75 mg contains as active substance 75 mg of acetylsalicylic acid, and is a white-coloured capsule.

The soft capsules are packed in Pentapharm Aclar/Aluminium blisters.

The excipients are:
capsule content - hydroxypropylbetadex, omega-3-acid-triglycerides, beeswax yellow (E 901), hydrogenated coconut oil, palm oil,
capsule shell - gelatin (E 441), sorbitol liquid partially dehydrated (E 420), dimeticone (E 900), hydroxypropylbetadex.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Excipients commonly used for the production of softgel capsules were tested separately or in combination with others. Disintegration of the capsules is the time consuming step and the dissolution of acetylsalicylic acid is fast. Therefore, the inclusion of disintegration time and not including dissolution testing in the specification is considered to be acceptable. A bioequivalence study has been performed with Cardioral 75 mg manufactured conform the final manufacturing process.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The capsules are manufactured by preparing a shell solution, followed by the manufacturing of the fill suspension. The fill suspension is then encapsulated with the shell solution.
The manufacturing of suspension capsules is considered to be a non-standard process. Process validation has been performed on three consecutive production-scale batches. All batches complied with the specification. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
Most of the excipients comply with the Ph.Eur. These specifications are acceptable. Hydrogenated coconut oil and palm oil are not described in the Ph.Eur. These two excipients are widely used in the food industry and are described in the FDA-list 'Inactive ingredients for approved drug products'. Therefore usage is considered to be acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight of the capsule and the fill, uniformity of weight of the capsule and the fill, disintegration, identity by HPLC and TLC, content uniformity, assay, salicylic acid content, impurities, microbiological quality and loss on drying..
The release and shelf-life specifications are identical with the exception of assay and salicylic acid content which are widened in the shelf-life specifications.
A dissolution test has not been included in the specification since disintegration of the capsules is the time consuming step and the dissolution of acetylsalicylic acid is fast. All methods and limits included in the specifications are considered to be acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided three pilot-scale batches stored at 25°C/60% RH (24 months) and 30°/65% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Aclar/Aluminium blisters.
A decrease in assay and an increase of salicylic acid during the long term conditions were observed. A photostability study demonstrated that the capsules are slightly sensitive to light.
Since no out of specification values were observed, a shelf life of 24 months could be granted with the storage condition *Store in the original package in order to protect from light and moisture*. Stability data of production-scale batches will be provided when available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Omega-3-acid triglycerides, beeswax and gelatine are the only materials from animal origin. TSE statements declaring the absence of risk material in the excipients have been provided.

II.2 Non clinical aspects

This product is a generic formulation of Cardegic 75 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of acetylsalicylic acid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Acetylsalicylic acid is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Cardioral 75 mg capsules, soft (IBSA Farmaceutici Italia S.r.L.) is compared with the pharmacokinetic profile of the reference product Kardegic 75 mg powder for oral solution (Sanofi-Aventis, France).

The choice of the reference product
The reference product Kardegic 75 mg from France is identical to the product that was marketed in the Netherlands. Certificates of analysis for both test and reference product have been provided.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open-label, randomised, two treatment, two period, two sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 24 healthy adult subjects (12 males/12 females), aged 18-44 years. Each subject received a single dose (75 mg) of one of the 2 acetylsalicylic acid formulations. The soft capsule was orally administered with 240 ml water. The powder for solution (reference medicinal product) was dissolved in 140 ml of mineral water and administered to the subject afterwards the glass was then rinsed twice with 50 ml water. The rinse was also drunk by the volunteers. Both medicinal products were administered after supervised overnight fasting for at least 10 hours. A standardised meal was served 6 and 11 hours after dosing. There were 2 dosing periods, separated by a washout period of 20 days.

Blood samples were collected pre-dose, at 10, 20, 30, 40 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose after administration of the products.

In addition equivalence of the test and reference product in terms of pharmacodynamics (platelet aggregation inhibition and serum TXB2 levels) after multiple once daily administration (day 15) and at other time points of acetylsalicylic acid (ASA) and salicylic acid (SAL) after single dose administration was investigated.
The volunteers returned to the clinical centre daily, under fasting conditions, to be administered 75 mg of either test of reference medicinal product for 14 days. Blood samples were collected pre-dose and at 24 hours post-dose on day 1, 7 and 14.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Pharmacokinetic results
All 24 subjects completed the two study periods and were used for statistical analyses as per protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of acetylsalicylic acid (ASA) under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	992 ± 248	1004 ± 251	1416 ± 739	0.67 (0.33-3)	0.4 ± 0.1
Reference	976 ± 244	986 ± 243	1594 ± 327	0.33 (0.17-0.5)	0.4 ± 0.0
***Ratio (90% CI)**	1.01 (0.95-1.09)	1.02 (0.95-1.09)	0.81 (0.68-0.95)	-	-
CV (%)	14.2	32.4	34.4	-	-

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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of salicylic acid (SAL) under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	18972 ± 6822	19094 ± 6868	5355 ± 1422	1.0 (0.5-3.0)	3.1 ± 1.5
Reference	17583 ± 7095	17687 ± 7171	5659 ± 1512	0.5 (0.33-1.0)	2.7 ± 0.9
***Ratio (90% CI)**	1.08 (1.06-1.12)	1.04 (1.06-1.12)	0.95 (0.90-1.00)	-	-
CV (%)	6.1	6.1	11.4	-	-

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

**ln-transformed values*

Pharmacodynamic results

The pharmacodynamic evaluation of TXB2 serum levels was studied in 12 out of the 24 subjects. Maximum percent TxB2 inhibition (I_{max}), extent of inhibition (AUC_{0-t}) and time at which maximum inhibition is achieved (t_{max}) were calculated and compared between formulations.

Table 3. Pharmacodynamic parameters (non-transformed values; arithmetic mean ± SD; t_{max}: arithmetic mean ± SD & median, range)) of TXB2 parameters after single dose administration under fasted conditions.

Parameter	Test	Reference	PE%*	95%CI
I_{max} (%)	80 ± 11	80 ± 11	100.02%	95.35-104.70%
AUC_{0-t}	1438 ± 561	1444 ± 615	99.71%	86.12-113.31%

T_{max} (h)	9 ± 7 6 (10 min-24h)	8 ± 7 6 (1-24)	--	--

*Point estimate: ratio of geometric means.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} both or acetylsalicylic acid and SAL are in agreement with those calculated by the MAH. The 90% confidence intervals for AUC_{0-t} and $AUC_{0-\infty}$ for ASA and AUC_{0-}, $AUC_{0-\infty}$ and C_{max} for SAL are within the 0.80-1.25 acceptance range. Robust pharmacodynamic data have been used to justify the clinical insignificance of C_{max} in this case. In addition, several ASA doses and formulations have been used in trials that established ASA's place as antithrombotic agent. Strict bioequivalence criteria to establish the pharmaceutical quality of the product are less relevant in this case due to the lack of one single acceptable reference product. In conclusion bioequivalence is sufficiently established with regard to the extent of absorption for ASA and rate and extent of absorption for SAL. In addition, non-inferiority has been demonstrated with respect to the maximum inhibition of TxB2. The I_{max} and AUC_{0-t} after administration of both products are statistically similar as the point estimates of the ratio's are very close to unity and the 95% confidence intervals are small.

Acetylsalicylic acid may be taken without reference to food intake. As stated in the SPC, simultaneous ingestion of food delays the absorption of acetyl salicylic acid (lower plasma concentrations) but does not reduce it. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Acetylsalicylic acid was first approved in 1957, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of acetylsalicylic acid can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. Fifteen questions were asked. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cardioral 75 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Cardegic 75 mg, powder for oral solution. Cardegic is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Robust pharmacodynamic data have been used to justify the clinical insignificance of C_{max} for ASA in this case.

The MAH will provide written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations (see commitment below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other acetylsalicylic acid containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cardioral 75 mg capsules, soft with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 December 2009. Cardioral 75 mg capsules, soft was authorised in the Netherlands on 24 February 2010 .

A European harmonised birth date has been allocated (5 January 1957) and subsequently the first data lock point for acetylsalicylic acid is February 2010. The first PSUR will cover the period from December 2009 to February 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 28 December 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to conduct stability studies under both real time and accelerated conditions on the first three industrial-scale marketing batches.

Pharmacovigilance

- The MAH committed to make all procedures available and implemented by the time the marketing authorization is granted.

List of abbreviations

ASA	Acetylsalicylic Acid
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CABG	Coronary Artery Bypass Grafting
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
CVA	Cerebrovascular Accident
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SAL	Salicylic Acid
SD	Standard Deviation
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached