CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kajodan 65 mg tablets
G.L. Pharma GmbH, Austria

potassium iodide

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/2481/001/MR
Registration number in the Netherlands: RVG 109973

23 May 2012

Pharmacotherapeutic group:	antidotes
ATC code:	V03AB21
Route of administration:	oral
Therapeutic indication:	to prevent the uptake of radioactive iodine in the thyroid after intake or inhalation of this substance after nuclear accidents with release of radioactive iodine isotopes
Prescription status:	non prescription
Date of first authorisation in NL:	14 July 2011
Concerned Member States:	Mutual recognition procedure with BG, CY, CZ, EE, FI, IE, IS, LT, LV, MT, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10a

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 Kajodan 65 mg tablets from G.L. Pharma GmbH. The date of authorisation was on 14 July 2011 in the Netherlands.

The product is indicated for use after nuclear accidents with release of radioactive iodine isotopes to prevent the uptake of radioactive iodine in the thyroid after intake or inhalation of this substance.

A comprehensive description of the indications and posology is given in the SPC.

The iodine released from iodide and iodate on absorption from the gut is taken up rapidly and preferentially by the cells of the thyroid gland. Once in the thyroid, it is rapidly incorporated into organic molecules that are synthesised into thyroid hormones and ultimately released into the general circulation.
If excessive amounts of stable iodate are administered to normal adults, the iodine uptake mechanism of the thyroid is saturated and little or no further iodine is taken up. This effectively blocks the uptake of radioactive iodine in the event of accidental exposure to radio-iodines.

This mutual recognition procedure concerns a so-called bibliographical application in accordance with article 10a of Directive 2001/83/EC. Potassium iodide is a well-known agent. It is recommended by the WHO as iodine prophylaxis for nuclear accidents.

This application concerns a bibliographical application based on well-established medicinal use of potassium iodide. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as no such plan is required for a bibliographical 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 potassium iodide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white powder or colourless crystals, and very soluble in water, freely soluble in glycerol and soluble in alcohol. Potassium iodide is an inorganic substance.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of two stages. No class 1 organic solvents or heavy metal catalysts are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

** 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
Kajodan contains as active substance 65 mg of potassium iodide, corresponding to 50 mg of iodide.The tablets are white to brown-white, round, curved tablets with a pressure-sensitive cross break line on the inner side and notches on the outer side. The tablet can be divided into equal quarters.

The tablets are packed in PVC-PVdC/Aluminium blisters.

The excipients are: maize starch, lactose monohydrate, microcrystalline cellulose, butylmethacrylate-(2-Dimethylaminoethyl)methacrylate-methylmethacrylate-copolymer, magnesium stearate (E572).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of the excipients was mainly based on avoidance of oxidation of potassium iodide. The main development studies regarded the development of a cross-score. The tablet can be subdivided into two and four equal fragments in compliance with the Ph.Eur. for optimal dosing. The MAH adequately demonstrated that subdivision of the tablets into halves and fourths complies with the Ph.Eur. requirement for subdivision of tablets. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard process that consists of pre-sieving and wet granulation, drying and sieving of the granulate, final blending and tablet compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, dimensions, identification, assay, loss on drying, sum of free iodate and iodine, resistance to crushing, disintegration, average mass, uniformity of dosage units and microbiological quality. Dissolution tests at different pH values demonstrated a rapid dissolution (more than 90% in 15 minutes) in three media. The release and shelf-life requirements are identical and are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on four full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided eight pilot scale and seven full scale batches stored at 25°C/60% RH (up to 120 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline for the majority of the stability batches. The batches were stored in PVC-PVdC/Al-blisters. Except for a significant and consistent change of loss on drying at accelerated conditions, no other changes or trends were seen. The proposed shelf life of 5 years and storage condition “Do not store above 25°C” are justified. The Ph.Eur. monograph on potassium iodide states that the drug substance should be stored protected from light. No photostability testing has been conducted; therefore the additional storage condition is “Store in the original package in order to protect from light”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE statement for lactose monohydrate is included in the dossier that states that it is produced from milk, sourced from healthy cows in the same conditions as milk collected for human condition. This is acceptable and considered safe. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This active substance has been available on the European market for many years. The MAH submitted a non-clinical overview of sufficient quality. Preclinical data have been superseded by clinical experience.

Environmental risk assessment
An environmental risk assessment is considered not necessary since both potassium and iodide are natural compounds which are widespread in the environment.

II.3 Clinical aspects

Introduction
This application concerns potassium iodide tablets 65 mg intended for use after nuclear accidents with emission of radioactive isotopes of iodine (predominantly 131I, but also 132I and 133I), to prevent or limit

radioiodine uptake by the thyroid gland after incorporation by ingestion or inhalation. Stable potassium iodide (KI) serves as a prophylactic agent. It takes effect at high doses far beyond physiological quantities, which block further iodine uptake and storage by the thyroid (Wolff-Chaikoff effect) for a certain period. Under these conditions radioiodine predominantly follows the renal elimination pathway. So the radioactive burden to the thyroid and the risk of radiation induced thyroid cancer are minimized.
As this application is under Art 10(a) well established use applicant did only submit a Clinical Overview. No clinical or pharmacokinetic studies were provided.

Pharmacokinetics
The clinical overview gives a good summary of the pharmacokinetics of iodide.
For not submitting pharmacokinetic studies the applicant gives the following justification in the Clinical Overview:

The drug substance belongs to Class I of the Biopharmaceutics Classification System (high solubility and high permeability), meets the criterion of rapid dissolution and contains well-established excipients which do not significantly affect the pharmacokinetics of the active substance. From the clinical point of view there is no risk of therapeutic failure, and safety aspects are unlikely to change over a dosage range considerably wider than intended for stable iodine prophylaxis.

This is agreed.

The distribution of iodide is rather complex as with all halide ions. Iodide in the systemic circulation exchanges rapidly with erythrocytes and the extracellular fluid. The total amount of inorganic iodide within the plasma pool is about 250 µg and subject to a fast turnover up to several times daily. The normal daily intake is 150 – 250 µg.
The elimination of iodide is mainly by the renal pathway through glomerular filtration and partial reabsorption, renal iodide clearance being 30 to 40 ml/min. More than 95% of the iodide excreted is found in urine. The renal elimination rate is not influenced by iodine intake or serum iodide levels.

Taken the fast dissolution, complete absorption, complicated distribution and elimination, potassium iodide can be considered as a Class I drug in the BCS and the influence of the pharmaceutical formulation (excipients, manufacturing process etc.) will only have a very small effect on the clinical efficacy.

Furthermore, as these tablets are only administered in case of an emergency and in a large overdose compared with the normal daily intake, clinical efficacy studies and pharmacokinetic studies are considered not necessary.

Pharmacodynamics
Mechanism of action
Potassium iodide serves as a prophylactic agent. It takes effect at high doses far beyond physiological quantities, which block further iodine uptake and storage by the thyroid (Wolff-Chaikoff effect) for a certain period. Under these conditions radioiodine predominantly follows the renal elimination pathway. So the radioactive burden to the thyroid and the risk of radiation induced thyroid cancer are minimized. The population intended for prophylactic administration of potassium iodide includes persons up to the age of 40 years. The intake of iodine tablets is not recommended for persons above 40 years because it has been determined that in this population there is no increased risk of thyroid cancer after exposition to radioactive iodine.

Other pharmacodynamic effects
Pharmacological doses of potassium iodide are used for the treatment of various thyroidal disorders, e.g. the preoperative preparation of toxic goiter, the treatment of thyroid storm and Graves' disease, and for non-thyroidal diseases, e.g. as an expectorant and as a systemic anti-infective agent for inflammatory dermatosis and dermatomycosis. Furthermore, iodine compounds are widely used as local disinfectants.

Interaction with other drugs

Concomitant administration of iodine-containing drugs (e.g. amiodarone) increases the overall iodine dose and thus the risk of toxic side effects. Interactions may occur if other thyroid-blocking agents are taken at the same time. Lithium salts prolong the residence time of iodine in the thyroid and may enhance the hypothyreotic effect and the development of goiter. The clinical effect of digitalis preparations seems to depend on the functional state of the thyroid, so serum levels may be altered by administration of excess iodine. Additionally, the interaction between digitalis and potassium levels has to be considered. Concomitant use of potassium-containing medication, potassium-sparing diuretics or angiotensin-converting enzyme inhibitors (ACE inhibitors) may lead to hyperkalaemia and potassium toxicity.

Clinical efficacy

The development of potassium iodide 65 mg tablets was initiated by the Austrian health authorities and is based entirely on published clinical data and the conclusions drawn by the WHO Regional Office for Europe in the Guidelines for iodine prophylaxis following nuclear accidents, published in 1989 and updated in 1999. Efficacy trials for this particular indication are associated with a particular risk arising from the use of radioactive tracer substances, so the clinical documentation is rather limited as compared to conventional medication. Retrospective studies in Poland after the Chernobyl accident give an impression of the use of Potassium iodide in a real emergency situation. Information available on the efficacy and safety of this substance was found to sufficiently cover all relevant clinical aspects, so further clinical trials were considered not justifiable from the ethical point of view.

Literature shows that the prophylactic effect is optimal if potassium iodide (iodine doses from 30 to 100 mg) is given prior to or at the time of exposure. If stable iodine administration is delayed, the blocking effect decreases as a function of time, but is still relevant even in case of an administration delayed by 12 hours.

Clinical safety

Potassium iodide is a substance of low toxicity which has been conferred the GRAS ("Generally Recognized As Safe“) status by the FDA. The incidence of adverse reactions is rather low. An increased incidence of toxic reactions is expected at daily doses exceeding 3.6 g. However, a clear dose proportionality is lacking for the lower dose range. Literature reports that a daily intake of up to 1000 mg iodine (1308 mg of potassium iodide) is probably safe for the majority of people, but may cause adverse reactions in some subjects.

Intrathyroidal adverse drug reactions (i.e. thyroiditis, iodide goitre and/or hypothyroidism, iodide-induced thyrotoxicosis / hyperthyroidism) after excess iodine may occur with or without pre-existing (latent) thyroid abnormalities, the latter being rather uncommon.

Most extrathyroidal adverse drug reactions take place after ingestion of high doses (> 3.6 g/day), e.g. after long-term use of amiodarone or iodine-containing expectorants, or by using potassium iodide for the treatment of inflammatory dermatosis and mycosis. Reported are: sialadenitis, gastrointestinal irritation, iodide fever, iodism (chronic intoxication) and reactions affecting the respiratory system.

Patients at risk for toxic reactions are those with renal insufficiency because of potential iodine accumulation resulting in higher serum concentrations than expected after ingestion of otherwise well-tolerated doses.

Clinical experience

The most extensive documentation of potassium iodide administration comes from the retrospective study reports by Nauman and Wolff (1993) on the Polish prophylaxis program after the Chernobyl accident in April 1986. No differences were observed between the treated and the unprotected control paediatric and adult group in long-term thyroid (dys)function and in the clinical course in case of pre-existing thyroid disease.

Vomiting was the most common adverse effect (mainly seen after administration of diluted iodine tincture). Additionally, minor skin rashes (approximately 1%) and a few cases of gastric irritation and diarrhea were reported. Four cases of thyroid pain were reported in adults, but none in children. Serious reactions (bronchospasms) were observed in two adults with chronic obstructive pulmonary disease and known iodine hypersensitivity, which is an absolute contraindication to potassium iodide prophylaxis. 4% (corresponding to 0.2% of the population studied) of all adverse reactions were considered medically significant.

Risk management plan

The safety profile of potassium iodide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. 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

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for other potassium iodide products available in Europe.

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 with 3 participants, followed by two rounds with 13 participants each. The questionnaire included 14 questions on patient-relevant topics in the PIL. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In total, 12 questions were answered by 100% of the participants.
The other two questions were by 96% of the participants. To further improve the leaflet, recommendations and suggestions by the participants on the wording and layout of the package leaflet were implemented where considered useful. These adaptations contribute to an improved understanding of the package leaflet. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kajodan 65 mg tablets has a proven chemical-pharmaceutical quality and is a well-established medicinal product. Based on the submitted dossier and further literature, Kajodan can be considered effective in the prevention or limitation of radioiodine uptake by the thyroid gland after incorporation by ingestion or inhalation after nuclear accidents with emission of radioactive isotopes of iodine. It is recommended by the WHO as iodine prophylaxis for nuclear accidents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

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

The Board followed the advice of the assessors. Kajodan 65 mg tablets was authorised in the Netherlands on 14 July 2011.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 5 April 2012.

The date for the first renewal will be: March 2016.

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

Quality – active substance

- The MAH committed to provide the validation report of the GC method, including the limits of detection of the methods showing that the various solvents mentioned were not detected.

Quality - medicinal product

- The MAH committed to provide an upper and lower hardness limit for the test resistance to crushing according to the Ph.Eur. method 2.9.8, if more batch data from stability testing are available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
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
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
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	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