LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kaliumjodid SERB
(potassium iodide)

SE/H/173/01/E/04

This module reflects the scientific discussion for the approval of Kaliumjodid SERB. The procedure was finalised on 2022-09-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Kaliumjodid SERB, 65 mg, tablet.

The active substance is iodine, potassium iodide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for product Kaliumjodid SERB, 65 mg, tablets, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, SERB S.A. applies for a marketing authorisation in AT, BG, CS, DK, EE, FI, HU, IT, LT, LV, PL, RO, SI, SK through this repeat use procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
The mechanism of action and iodine thyroid blocking treatment in association to nuclear accident is well established. No safety pharmacology has been discussed by applicant, however, these deficiencies are acceptable provided that the clinical safety profile is well-known.

Pharmacokinetics
No conventional pharmacokinetic study was presented, however, the distribution pattern and excretion pathways are well known. This is considered acceptable.

Toxicology
Repeated dose toxicity
The objective of the present study was to explore the influence of excess iodide exposure on carbohydrate and lipid metabolism along with the histoarchitecture of certain associated organs such as the pancreas, liver, kidney, and skeletal and cardiac muscles.

Twelve rats were included in a repeated toxicity study, six were fed with iodine through gavage at a dose of 3.5 mg KI /100 g body weight, which corresponded to 500 times of the physiological daily dosage of iodide for a period of 60 days, and six were used as the control group. In conclusion, excess iodine exposure for a long duration causes the development of a biochemical state of hypothyroidism. The developed hypothyroidism was found responsible for a hyperglycaemic and hypercholesteraemic status evident by high blood glucose and cholesterol levels and a depletion of glycogen at its storage sites in the liver and skeletal muscle but extra deposition in the cardiac muscle and kidney; histomicrophotographs showed severe destruction of the pancreatic structure. All these alterations are conducive for the pathogenesis of cardiovascular and kidney diseases.

Genotoxicity
KI is not likely to be classified as mutagenic *in vitro* according to a micronucleus assay on Chinese Hamster Ovary (CHO) cells.

The level of oxidative damage to nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) isolated from porcine thyroid under basal conditions was studied in the presence of Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\cdot}OH + OH^-$) substrates. Thyroid nDNA and mtDNA were incubated in the presence of either KI or KIO_3 (2.5–50 mM), without/with $FeSO_4$ (30 μM) + H_2O_2 (0.5 mM). The concentrations corresponded to those typical for Wolff–Chaikoff effect. Neither KI nor KIO_3 increased the basal level of 8-oxodG in both nDNA and mtDNA. KI—in all used concentrations—both components completely prevented the damaging effect of Fenton reaction substrates in mtDNA, and partially prevented this damage in nDNA.

*C**arcinogenicity***
In a 2-year carcinogenicity study in F344/DuCrj rats, squamous cell carcinomas (SCCs) were observed in the salivary glands of 4/40 males and 3/40 females receiving 1,000 ppm KI in the drinking water. Ductular proliferation with lobular atrophy was observed at high incidence in the submandibular glands of the high-dose animals, and squamous metaplasia was frequently evident within the proliferative ductules and the larger interlobular ducts. A transition from metaplasia to SCC was apparent.

In a combined carcinogenicity and chronic toxicity study, KI was orally administered in 0, 10, 100 or 1,000 ppm in drinking water to male and female F344/DuCrj rats. These doses are equivalent to approx. 0.55. 5.31 or 55.03 mg/kg/day in males, and approx. 0.66, 6.73 or 66.59 mg/kg/day in females. The incidence of thyroid follicular dilatation was increased in the 10, 100 and 1,000 ppm groups of both sexes. The results showed no systemic toxic effects, however, a depression in body weights and induction of squamous cell carcinomas in the salivary glands were observed at 1,000 ppm. Carcinogenicity assessment was conducted in rats who were administered 0 or 1,000 ppm of KI for 83

weeks following a single injection of N-bis(2-hydroxypropyl) nitrosamine (DHPN). Squamous cell carcinomas were induced in the salivary glands of the KI 1,000 ppm group, but no tumours were observed in the thyroid. Thyroidal weights and the incidence of thyroid tumours derived from the follicular epithelium were significantly increased in the DHPN+KI as compared with the DHPN alone group. These results suggested that excess of KI has a thyroid tumour-promoting effect, but KI per se does not induce thyroid tumours in rats. In the salivary gland, KI was suggested to have carcinogenic potential via an epigenetic mechanism, but only active at a high dose i.e. 1,000 ppm.

Reproductive and developmental toxicity
Pregnant Wistar rats were given a 1 % (w/v) or a 0.1 % (w/v) solution of KI in drinking water. Rats given the 0.1 % KI solution had normal fluid intake, maintained healthy litters and had a high rate of implantation. Rats receiving 1 % KI had severe adverse effects; none of the six rats had implantation sites at autopsy.

The effect of ingestion of KI on the behavioural competence of developing Sprague Dawley rats before and during breeding, to females only during gestation and lactation was studied in the dose levels of 0, 0.025, 0.05 or 0.1 % (w/w). Dams in a positive control group were given 4 mg/kg intraperitoneally of the anti-mitotic/cytotoxic drug 5-azacytidine on day 17 of gestation. Maternal toxic effects showed a LOAEL value at 90 mg/kg/day (0.1 %). At this dose level, KI did not produce any significant reduction in parental body weight or food consumption.

Embryotoxic/ teratogenic effects:
- Litter size was significantly reduced, but birth weights and external morphology among those born alive were not significantly altered.
- KI produced significant increased mortality in offspring in the 0.1 % (w/w) group at birth and up to day 24 after birth.
- KI decreased body weights in both the 0.1 and 0.05 % (w/w) groups in both males and females and were significant on days 14 and 21 in the test chemical groups. There were no significant weight reductions found in the 0.025 % (w/w) group.
- No significant effect was found on absolute or relative thyroid weight at 90 days of age.
- For the F1 generation, the LOAEL value for KI was found to be about 45 mg/kg/day (0.05 %), based on the effect of decreased pre-weaning body weights in the offspring, delay in auditory startle and delayed olfactory orientation from the home-cage scent.
- In rats killed on day 90 after birth, KI reduced brain and body weight at a dose of 0.1 % of the diet, and reduced body but not brain weight at a dose of 0.05 % of the diet.
Overall, the data in this experiment support the view that KI at doses of up to 90 mg/kg/day (0.1 %) in the diet of growing rats produces evidence of reproductive and developmental toxicity.

Mahapatra and Chandra 2017 investigated the effect of excess iodine (EI) on the ovarian physiology of 120 female healthy adult rats. The animals were divided into three groups, one control group, and two test groups; 0.7 mg (100IE) or 3.5 mg (500IE) KI/100 g bw (100 and 500 x recommended dose) orally for 60 days. Oestrous cyclical changes, ovarian morphological changes, ovarian iodine accumulation and ovarian steroidogenic enzyme activities were analysed. The thyroid functional status was studied from the serum thyroid hormones levels.
The overall results revealed a biphasic action of excess iodine that depends on its dose.
- At 100 EI, excess iodine did not alter thyroid physiology but lead to the development of a hypoestrogenic state. There was an increased accumulation of iodine in the ovary with decreased activity of ovarian steroidogenic enzymes and lowered serum oestradiol levels.
- At 500 EI, excess iodine developed a hyperthyroid condition, which further leads to a hyperoestrogenic state. There was an increased activity of serum steroidogenic enzymes as well as elevated serum oestradiol levels.
- Fertility index was zero in both the 100 EI and 500 EI treated groups of experimental animals.

In conclusion, excess iodine ingestion within tolerable range (100 EI) maintained a euthyroid condition but developed a state of hypofunctioning ovary. Conversely, excessive iodine (500 EI) is

intolerable to thyroid and induces the development of a hyperthyroid condition that leads to a hyperfunctioning ovary. Both doses used in this study affected fertility equally.

Other studies have been reported in ECHA database [ECHA 2019]:

The effect of the KI on the reproductive performance of female minks was investigated. Female minks were administered with 0, 10, 100, or 1,000 ppm of KI, in diet for 18 days, from breeding through lactation. No detrimental effects were observed on litter size or kit survival in the group fed with 10 ppm of KI, and hence the NOAEL for reproductive toxicity in female minks is determined to be 10 ppm of the test chemical in the diet.
Another study was conducted in 27 rats to determine the effects of KI intake. Females were bred to normal males, wherein KI was added to the diet (unspecified dosage) during the latter portion of gestation and the females were permitted to litter normally. Gestation time for rats was not affected; however, prolonged parturition was observed in rats. In foetal parameters, average mortality was slightly greater of young from those fed with the KI, while the weaning weight was significantly less than that of controls.
In another experiment, the female rats were re-bred after removal of dietary intake of the test chemical. It was observed that the females gave birth and nursed litters normally. From all the above observations, LOAEL was found to be 150 mg/kg, and it is likely to be regarded that there is no reproductive toxicity at concentrations lower than 150 mg/kg when administered orally.

The last study was a one-generation and fertility reproductive study, where pregnant female Wistar rats were given fluid orally on a regular basis at dose levels of 0.1 % (w/v) or 1 % (w/v) of KI.
The main results were:
- Treatment with 1 % (w/v) solution led to reduced body weight and fluid intake, adrenal glands were enlarged, and the level of implementation was prevented.
- No change in food or fluid intake was seen for rats treated with 0.1 % (w/v) solution.
- In addition, the 0.1 % (w/v) solution-treated rats showed a high rate of implantation.

Since 0.1 % (w/v) of KI is regarded as a high value intake and it was concluded that KI has no effect on reproductive toxicity when orally administered.

Impurities and excipients of Potassium iodide SERB
The drug product at shelf-life, the impurities iodate and free iodine are limited to 4 ppm.
These specifications are in accordance with the Note for Guidance on Impurities in New Drug Products [CPMP/ICH/2738/99, June 2006]. The excipients comply with the appropriate monographs of the current edition of the European Pharmacopoeia.

The non-clinical toxicology data presented is acceptable provided that the clinical safety profile is well known.

Environmental Risk Assessment (ERA)
Since potassium and iodine are natural occurring elements, the introduction of this product to the market will not lead to an increased exposure to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics

- **Potassium pharmacokinetics**

The absorption of K^+ in the human gastrointestinal tract is by passive diffusion. The plasma protein binding of K^+ is negligible. Reportedly about 90% of an oral dose of K^+ is eliminated by the renal route, and the remainder by the faecal route, in healthy subjects. The renal excretion of total K^+ is by

glomerular filtration, reabsorption in the proximal tubule, and secretion in the distal tubule. Under normal conditions there is net tubular reabsorption of K^+.

- **Iodide pharmacokinetics**

Absorption

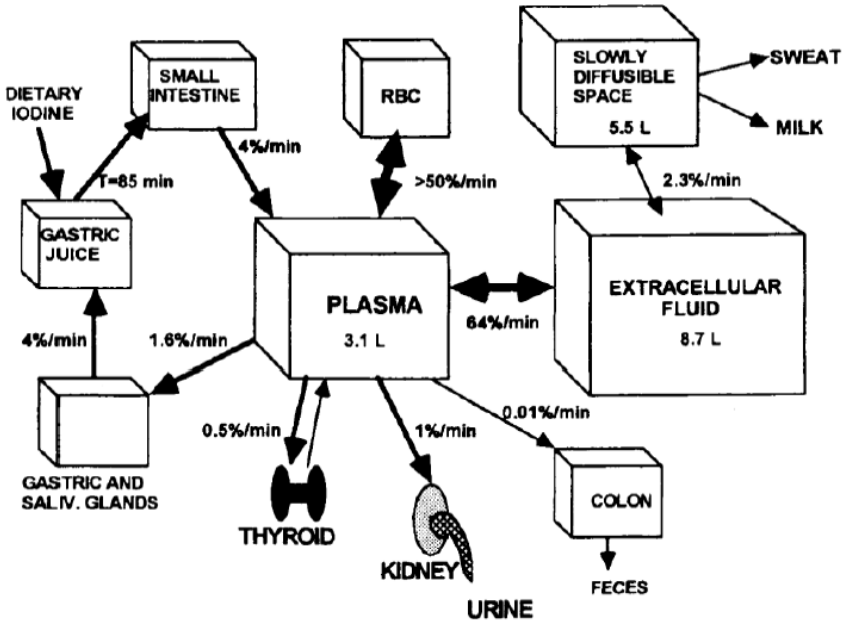
Due to the high solubility of iodide in water, intestinal absorption begins as soon as iodide reaches the stomach. Absorption is fast and complete in almost all subjects, within a maximum of 2 hours after oral administration.

In a fasting subject, iodide radioactive tracer I-131 is observed in the neck area approximately 3 minutes after oral administration. Food in the stomach delays absorption by roughly 10 to 15 minutes.

Distribution

Iodine distribution is complex. Multi compartmental distribution of dietary iodine has been postulated (figure 1). As dietary iodine is converted mostly in iodide (I^-) in the gut before absorption, this model can be extrapolated to iodide distribution after KI tablet intake. Iodide in the systemic circulation exchanges rapidly with erythrocytes and the extracellular fluid. Total plasma iodine concentrations in euthyroid subjects range from 40 to about 80 µg/L. Then, iodide follows two principals, competitive pathways: uptake by the thyroid gland or excretion in urine.

Figure 1. Compartmental model of inorganic iodine distribution.



RBC: red blood cells

Iodide thyroid uptake

After a single ingestion of radioactive labelled iodine, thyroid uptake begins rapidly and then, in euthyroid subjects, reaches a plateau at 10% to 40% of the total iodine ingested in 24 to 48 hours. The time to reach half the total thyroid uptake varies from 3 to 6.5 hours with substantial interindividual variation.

Thyroid clearance depends on the volume and activity of the gland. It is adaptive and depends on plasma iodide concentration and dietary iodine intake. As a result, when dietary iodine intake is low, thyroid uptake increases. Thyroid uptake depends also on the physiological age, it is higher in adolescents than adults and decreases progressively with age.

Iodide uptake by extrathyroidal tissues

Besides the thyroid, active iodide transport also occurs in extrathyroidal tissues such as salivary

glands, gastric mucosa, choroid plexus and in mammary glands during lactation, but to a minor extent. Iodine also crosses the placenta and is taken up by the foetal thyroid, which begins concentrating iodine and synthesizing thyroid hormones after 12 weeks of gestation.

Metabolism
Iodide undergoes organification in the thyroid, being oxidized and linked to thyroglobulin. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are then synthetized via oxidative condensation of the iodinated intermediates monoiodotyrosine (MIT) and diiodotyrosine (DIT) inside the thyroglobulin complex.

Excretion
The kidney is the main route of excretion of iodide. In adults with adequate iodine intake, the excess iodine not taken up by the thyroid is excreted in the urine (more than 90 % of dietary iodine), with partial reabsorption occurring in the renal tubules.
The renal iodide clearance is 30–36 mL/minute in euthyroid subjects and is significantly decreased either in impaired renal function or in myxoedema.
Small amounts of iodides are also excreted in the faeces, saliva, and sweat.
In breastfeeding women, there is an increased elimination of iodide, excreted into breast milk in large amounts decreasing progressively during the first 6 months of lactation.

Pharmacokinetic interactions
No pharmacokinetic interactions are expected with KI. (For pharmacodynamic interactions see the respective section below)

MPA conclusions on pharmacokinetics
The MAH has provided sufficient/adequate data on the pharmacokinetics of KI considering the specificity of the drug product, i.e., small-molecular ionic compound. Overall, available pharmacokinetic data are adequately reflected in the SmPC.

Pharmacodynamics

Mechanism of action
At high doses such as those recommended for KI treatment in case of a radioactive or nuclear accident, iodide acts immediately to block further uptake of iodide by several means, particularly by saturating the iodide transport mechanisms of the thyroid via competition, by inhibiting the intrathyroidal organification of iodide (Wolff-Chaikoff effect), and by simple dilution.

Iodide uptake by the thyroid gland is saturable, specific and the rate-limiting step of hormone synthesis. It is mediated by the sodium iodide symporter (NIS), an active transporter which limits iodine accumulation in the thyroid. These transporters are located at the apical membrane of the thyroid follicular cells where iodide is translocated into the colloid and organified, that is, oxidized and then combined with the tyrosine residues of thyroglobulin. Iodine uptake and organification are stimulated by thyrotropin (TSH).

Iodide itself is a major regulator of iodide accumulation and organification by the thyroid. Iodine intake inhibits the expression of NIS transporters.

Further, a sudden iodine overload paradoxically blocks the second step of hormone synthesis in the thyroid gland and blocks the incorporation of iodide into the tyrosyl residues of thyrotropin, the first step in thyroid hormone biosynthesis (organification). This TSH-independent autoregulatory block (Wolff-Chaikoff effect) relies on a high (≥ 10-3 molar) intracellular concentration of iodide. However, the Wolff-Chaikoff block is short lived, because the biosynthesis of NIS is rapidly shut down, intracellular iodide drops below 10-3 molar and organification of iodine resumes. It appears several hours after an excess dose of iodine, but iodine organification by the thyroid resumes within 24 to 48 hours, even if the iodine overload persists (escape).

Pharmacodynamic interactions

Concomitant use of potassium-containing medication such as angiotensin-converting enzyme (ACE) inhibitors or potassium-sparing diuretics (amiloride or triamterene or aldosterone antagonists) with KI may result in hyperkaliaemia and cardiac arrhythmias or cardiac arrest; serum potassium concentrations should be monitored to avoid potassium toxicity. However, usual doses of KI used for radiation protection (i.e., up to 130 mg) contain negligible amounts of potassium and should not constitute a problem with ACE inhibitors however caution is required.

Concomitant use of lithium with KI may potentiate the hypothyroid and goitrogenic effects of either medication; baseline thyroid status should be determined at periodic intervals to detect changes in the thyroid-pituitary response.

Concomitant use of antithyroid agents with KI may potentiate the hypothyroid and goitrogenic effects of antithyroid agents or KI; baseline thyroid status should be determined at periodic intervals to detect changes in the thyroid-pituitary response.

Concomitant administration of iodine-containing drugs (e.g., amiodarone) increases the overall iodine dose and thus the risk of toxic side effects.

MPA conclusions on pharmacodynamics

The MAH has provided adequate data on the mechanism of action of KI in the indication "*prophylaxis of radioactive iodine absorption on the thyroid gland in case of nuclear accident*". The pharmacodynamic data, including information on pharmacodynamic interactions, is adequately reflected in the SmPC.

Clinical efficacy

The current application is supported by retrospective observational studies, reports and guidelines from scientific bodies and expert opinions. No data from recent clinical trials is included, due to the fact that KI is approved for prophylaxis of radioactive iodine absorption on the thyroid gland in the exceptional case of a nuclear accident.

Clinical data presented within this application focus on two major efficacy outcomes:

1. The short-term outcome of KI protective effect upon thyroid uptake of radioiodine.
2. The long-term outcome of KI protective effect against the development of thyroid cancer.

Studies on KI protective effect upon thyroid uptake of radioiodine

A few clinical studies performed on healthy subjects allowed to determine KI optimal dose and timing of administration upon radioactive iodine release.

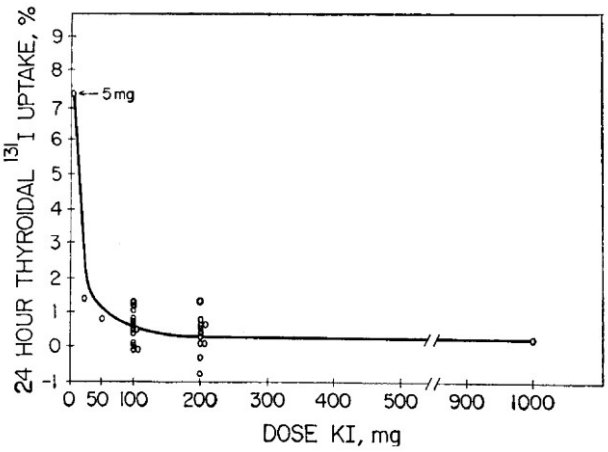
The basal thyroid uptake of radioactive iodine I-131 was investigated in 62 healthy volunteers (37 men and 25 women) aged from 21 to 72 years. The percentage of thyroid I-131 accumulation was determined 24 hours after the administration of a standard dose of 1.5 nanocuries of sodium iodide I-131.

Among those 62 subjects, the effect of KI administration on thyroid I-131 accumulation was investigated in 41 subjects (24 men and 17 women). These subjects received doses of stable KI (I-127), ranging from 5 to 1,000 mg, either one hour prior to, with, or at specified times following administration of the radioactive iodide I-131. One or two days later, an additional dose of 1.5 to 5 nanocuries of the radioactive agent I-131 was administered without a further dose of KI, and the 24-hour uptake was again measured to evaluate the duration of the suppressive effect. The extent of uptake blockade was estimated by measuring serum inorganic iodide.

Dose-efficacy relationship
The average uptake of I-131 in the 62 volunteers was 27.1% of the received dose in 24 hours, with a standard deviation (SD) of ± 8.9%.

In the 41 subjects who took KI, the ability of the thyroid to accumulate radioactive iodine was progressively reduced when increasing dose administered with the radioactive compound. The average I-131 uptake after 100 and 200 mg of potassium iodide was 0.6 ± 0.5 % (n=14) and 0.3 ± 0.3 % (n = 10), respectively (Figure 2). Serum concentrations of inorganic iodide greater than 10 µg /100 mL correlated with marked uptake arrest.

Figure 2- Thyroid 24-h I-131 uptake when KI is co-administered with sodium iodide I-131



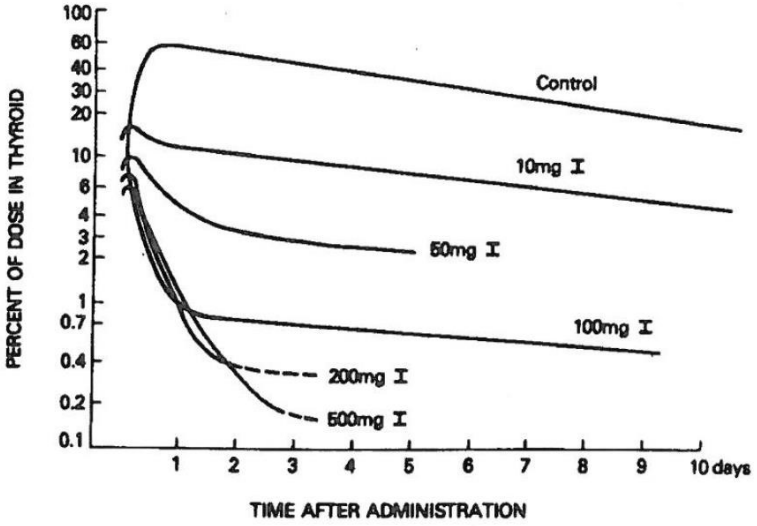
Timing of administration
The dose of 200 mg of KI was given at different time intervals before, with or after I-131 absorption. The blockade of radioiodine uptake was progressively less effective but was still reduced to less than 50% after a delay of 3 hours. The blocking agent was also most effective if given with or just before exposure to radioactive iodine.

The extent of suppression was sharply reduced when the KI was given 48 hours before the radioactive compound. Iodide is rapidly excreted by the kidney from the extrathyroidal pool, accounting for the short duration of protection afforded by a single ingestion. Therefore, in the event of prolonged exposure to radioactive iodine, the authors advocated for a daily re-administration of the agent for prolonged protection.

In another study, the dose-efficacy relationship, the protection against repeated exposure to I-131 and the timing of administration was investigated.

Dose-efficacy relationship
Various doses of iodide given as KI given to healthy volunteers simultaneously with a tracer dose of I-131, and their protective effect on the radioactive iodine uptake was measured over a 10 days-period (Figure 3). When administered simultaneously with the radioactive compound, the dose of KI 100 mg allowed to reduce the uptake to less than 1%.

Figure 3: KI protective effect against I-131 thyroid uptake



Protection against repeated exposure to I-131
Volunteers received radioactive I-131 daily for 2 weeks, and KI was given during the first week at different dosing regimen (Table 1). The protective effect was similar for 100 mg (daily or twice a day) and for 200 mg (daily, every 2 days or every 3 days). Moreover, despite one week of treatment, the protective effect was not better with one KI single dose.

Table 1 - Protection against repeated exposure to I-131 by KI

Iodide treatment schedule (mg)	Absorbed dose of daily I^{131} [a] (rad)	Protective effect[b] (%)
Control (no KI)	22.0 ± 1.5	
10, daily	3.0 ± 1.3	87.6
100, daily	0.75 ± 0.18	96.6
100, 2 × daily	0.50 ± 0.02	97.7
200, daily	0.30 ± 0.05	98.6
200, every 2 days	1.0 ± 0.12	95.5
200, every 3 days	2.5 ± 0.35	88.6

[a] Volunteers received ^{131}I daily for 2 weeks. KI was given during the first week only, the second week affording a period of unblocking.

[b] $\text{Protective effect} = \frac{\text{Absorbed dose (control)} - \text{Absorbed dose (blocked)}}{\text{Absorbed dose (control)}} \times 100.$

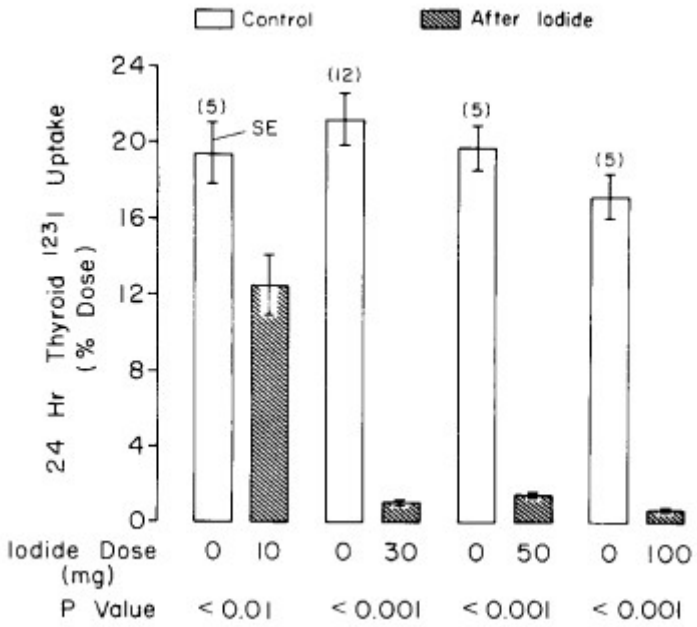
Timing of administration
The dose of 100 mg of KI was given at different time intervals before, with or after I-131 absorption, and the protective effect was calculated. The results are shown below in *Figure 5*.

In a study investigating the dose-efficacy relationship, the effect of various doses of sodium iodide on thyroid radioiodine uptake was investigated in 22 adult euthyroid volunteers (age from 23 to 50 years). First, baseline determinations of thyroid uptake of I-123 were carried out, and blood samples were obtained. One week later, a repeat tracer dose of I-123 was given, followed one to five minutes later by administration of various doses of stable iodide, and repeat studies of uptake were carried out.

Single doses of 10, 30, 50, and 100 mg were given the first day, followed by daily doses of 10, 15, 30, 50, or 100 mg for 12 days thereafter.

All single doses above 10 mg suppressed 24-hour thyroid uptake to 0.7 to 1.5 per cent (Figure 4). Continued daily administration of 15 mg of iodide or more resulted in values consistently below 2%. The authors concluded that the thyroid uptake of radioactive iodine can be markedly suppressed by single-dose administration of 30 mg of stable iodide, and that suppression can be maintained with daily doses of at least 15 mg.

Figure 4- Effect of Different Single Doses of Iodide on 24-Hour Thyroid Uptake of I-123



An expert's opinion paper describing the physiological basis for the use of KI as a thyroid blocking agent was published in 1983. The main clinical studies on the subject published at that time were summarized in this publication.

In this opinion paper, studies' results on the protective effect of 100 mg of KI according to the time of administration upon radioiodine thyroid uptake are plotted (Figure 5):

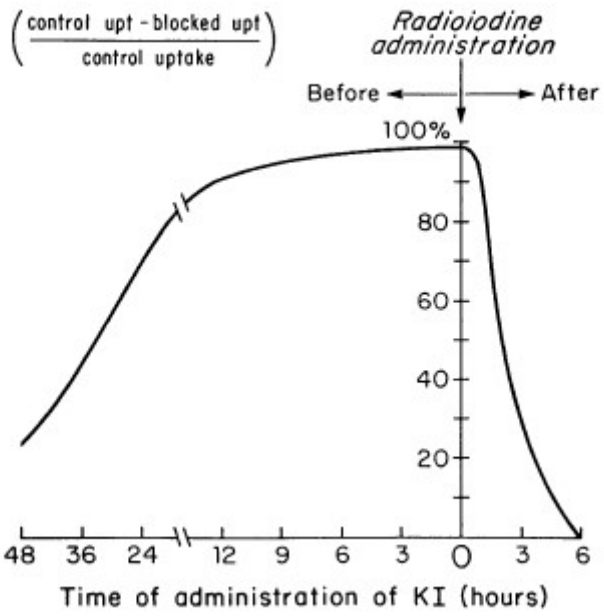
- If KI is given simultaneously with the radioiodine, the protective effect is about 97%, which means that only 3% is taken into the thyroid.

- If the KI is given 12 hours before radioiodine administration or exposure, protection is still excellent, approximately 90%.

- On the other hand, if the KI is given one hour after radioiodine, protection is only 85%, and by three hours the protective effect is down to about 50%.

- Giving KI six hours after radioiodine exposure has negligible protective effect.

Figure 5 - Protective effect of KI (100 mg) on thyroid uptake



It was concluded that this time relationship emphasizes the necessity of an early accessibility to KI to maximize its blocking effect. For this purpose, it should probably be distributed in advance.

Studies on KI protective effect against development of thyroid cancer

A survey study describing the outcomes of KI treatment during the polish prophylaxis program after the Chernobyl accident in 1986 has been published. In this extensive clinical experience, the Polish government ordered the preparation of KI by its national pharmacies 3 days after the accident when they first learned of the radioactive releases and were able to estimate the amount of radioiodine air contamination. Within hours, the KI was bottled, and distribution begun, and within 24 h, 75% of the children had received KI (as tincture or tablet). Overall, approximatively 10.5 million children (95.3% of the population) up to the age of 16 years, and 7 million adults (23.2%) received KI the fourth day after the accident.

The dosing recommendations were:

- 15 mg for new-borns
- 50 mg for children of 5 years or under
- 70 mg for all others

Because the cancer risk for adults was believed to be low, and some side effects (e.g., in persons with nodular goitre) might be anticipated, iodide prophylaxis was not recommended for adults; Iodide prophylaxis was recommended for pregnant and lactating women but was not mandatory.

Follow-up studies were then performed in specific groups of populations:

Children
A total of 12,084 children were assessed in a 10-years' follow-up study (1989 to 1990).

At the end of the study, no readily detectable long-term thyroid dysfunction could be observed in this study group: 91.4% of the children had normal TSH levels, 4.7% had lower levels and 3.9% had higher levels than the reference range of 0.3 to 3.8 mIU/L. Compared to an unprotected population (557 children who did not received KI prophylaxis), no significant difference on thyroid function was observed.

In 120,000 to 140,000 new-borns in 1985, 1986, and 1987, the incidence of congenital hypothyroidism was found unchanged. 12 (0.37%) out of 3214 new-borns who received KI prophylaxis on the second day of life, showed a transient increase in serum TSH and decreased free serum thyroxine, remaining without known sequelae up to 1993.

Adults
In 5,051 adults without pre-existing thyroid disease who took KI prophylaxis, TSH, thyroid hormone and antithyroid antibody levels were similar to those measured in 16,569 adults who did not take KI treatment.

In 774 adults with pre-existing thyroid disease who took KI prophylaxis, no case of exacerbation of hyperthyroidism or induction of thyrotoxicosis (with pre-existing nodular goitre) was observed. Compared to an unprotected control group (1,282 adult), no significant difference was observed

In conclusion, this study describes the largest clinical experience ever studied after a single pharmacologic dose of KI for prophylaxis of radioactive iodide absorption, including 12,084 children and 5,825 adults (774 with pre-existing thyroid disease). Overall, no thyroid dysfunction (i.e. thyroid cancer) has been observed in the studied population over the 10 years follow-up period when taking KI tablets.

In 2016, a systematic review of the literature was performed to evaluate the effects of KI administration in the case of accidental radioactive iodine release, on thyroid cancer, hypothyroidism and benign thyroid nodules occurrence.

The review used the PICO (Population, Intervention, Comparison, Outcome) methodology to answer to the following specific question: In a population exposed to radioiodine release (P), does the administration of KI for prophylaxis (I) versus no administration of KI (C) affect the risk of relevant outcomes, including thyroid cancer, hypothyroidism, and benign thyroid nodules (O).

The systematic review found 4 eligible studies.

The characteristics of the 4 studies are summarized in the following table.

Study number	**Location**	**Study design**	**Population**	**Interventions**	**Outcomes**
1	Poland	Cross-sectional study	1,457 subjects 6–55 years of age	Iodine prophylaxis	-Anti-human thyroid membrane antibodies (ATMA) -Anti-thyreoglobulin antibodies (TGAb)
2	Russia	Case-control study	276 case patients with thyroid carcinoma - 1,300 control subjects < 15 years of age at Chernobyl accident Resided in Russia	Potassium iodide as antistrumin	Thyroid cancer

Study number	Location	Study design	Population	Interventions	Outcomes
3	Ukraine	Analytic cohort	Individuals with direct thyroid radioactivity measurements - < 18 years of age on 26 April 1986 Resided in Ukraine	Iodine prophylaxis	Thyroid cancer
4	Poland	Case-control study	297 case patients with thyroid carcinoma 589 healthy control subjects 0–85+ years of age	Iodine prophylaxis (Lugol's solution)	Thyroid cancer

The 4 eligible studies were all related to the Chernobyl accident. Participants were from Ukraine, Belarus and the Russian Federation, and Poland. The number of participants ranged from 886–12,514.

There was no overlap in the studied populations. Participants from the studies in Poland were from two different areas, namely Suwalki province and Olsztyn province.

Three of those studies evaluated the prevalence of thyroid cancer:

- Study 2 reported a statistically significant threefold reduction (ORadj 0.31, 95% 0.1 – 0.9) in the odds of thyroid cancer at 1 Gy in the group who took KI (possibly at rather low doses) compared to the reference group. This low OR was independent of soil iodide content in the respective area of residence. Based on data provided from the study authors, a simple case-control analysis resulted in an OR of 0.38 (95% CI 0.20 – 0.70).

- Study 3 investigated the effect modification of the excess relative risk (ERR) of incident thyroid cancer per Gy of exposure according to KI intake. The effect modification was not significant (p = 0.56), with an ERR per Gy of 2.11 (95% CI 0.36 – 9.28) for no KI administration vs. 1.03 (95% CI 0.08 – 9.84) for KI administration. Based on data given per person years, the unadjusted relative effect of thyroid cancer after KI intake OR was of 0.68 (95% CI 0.36 – 1.28).

- Study 4 did not find significant differences in intake of KI in those who were diagnosed with cancer compared to the control group. Of the case patients with thyroid cancer, 31% had taken KI, while in the control group, 34% had taken KI. The respective OR was calculated as 0.87 (95% CI 0.65 – 1.18) for thyroid cancer after KI intake.

The results of this review suggest that KI administration following a nuclear accident may reduce the risk of thyroid cancer after exposure to radioactive iodine, particularly in children. However, this judgement was based on a small number of studies that provide low or very low quality evidence.

Moreover, the dosage and timing of KI administration in the study on persons who were aged < 18 years at the time of the Chernobyl accident were not well defined, and KI was potentially used at low doses. Therefore, these results need to be interpreted with caution.

There was also no evidence on the outcomes on hypothyroidism and benign thyroid nodules. Overall, the results of this systematic review have been taken into account for the 2017 update of WHO guideline on Iodine Prophylaxis following Nuclear Accidents [WHO 2017].

Clinical efficacy data from reference guidelines
Dosing regimen was defined on the predicted exposure levels of the population groups (i.e., intervention/action levels) [WHO 1999; EC 2010]. Doses further vary to account for the respective risks of vulnerable population groups (new-born, children and adolescents, and pregnant and lactating women).

The effective blocking of the thyroid is thought to be achieved with a single dose of 130 mg of KI in adult. Fractions of these quantities are suggested to be used in specific population groups in WHO 1999, FDA 2001 and EC 2010 guidelines. In 2017, dosage information has remained unchanged. The following single doses per specific population group are recommended (Table 2):

Table 2 - Recommended single dosage of stable iodine according to age group (adapted from [WHO 2017])

Age group	**Mass of iodine, mg**	**Mass of KI, mg**	**Fraction of a KI 65 mg tablet**
Neonates (birth to 1 month)	12.5	16	1/4
Infants (1 month to 3 years)	25	32	1/2
Children (3 to 12 years)	50	65	1
Adult and adolescent (over 12 years)	100	130	2

The groups most likely to benefit from ITB are children, adolescents, pregnant and breastfeeding women, whereas individuals over 40 years of age are less likely to benefit from ITB [WHO 2017].

Although KI administration blocks the thyroid, it does not provide complete protection from accumulating radioactive iodine. A single dose approximately blocks the thyroid for between 24 h and 36 h but the blocking capacity decreases with increased time after administration [FDA 2001; EC 2010].

Method of administration
The optimal period of administration of stable iodine is less than 24 hours prior to, and up to 2 hours after, the expected onset of exposure; It would still be reasonable to administer ITB up to 8 hours after the estimated onset of exposure [FDA 2001; EC 2010; WHO 1999; WHO 2017].

Starting ITB later than 24 hours following the exposure may do more harm than benefit (by prolonging the biological half-life of radioactive iodine that has already accumulated in the thyroid) [FDA 2001; EC 2010; WHO 1999; WHO 2017].

A single administration of stable iodine is considered as usually enough [FDA 2001; EC 2010; WHO 1999; WHO 2017].

However, in the case of prolonged (beyond 24 hours) or repeated exposure, unavoidable ingestion of contaminated food and drinking water, and where evacuation is not feasible, repeated administration of stable iodine may be necessary. Neonates, pregnant and breastfeeding women and older adults (over 60 years), should not receive repeated ITB [FDA 2001; EC 2010; WHO 1999; WHO 2017].

MPA conclusion on clinical efficacy
Due to the nature of the proposed indication, *prophylaxis of radioactive iodine absorption on the thyroid gland in case of nuclear accident*, no state-of-the-art-clinical trials or observational studies

have been performed. Thus, from an ethical perspective, randomised controlled clinical trials are not feasible. This has also been acknowledged by the WHO in its most current guideline.

The effectiveness of stable iodine in blocking thyroid uptake of radioactive iodine has been established in mechanistic and observational studies. The KI efficacy as a thyroid uptake blocking agent in case of exposure to radioactive iodine has been demonstrated in a few experimental clinical studies in healthy volunteers. These studies have shown that a dose of 100 to 200 mg of KI, administrated less than 24 hours prior to, and up to 2 hours after the exposure, is sufficient to almost completely saturate the thyroid with stable iodine, thereby protecting from radioactive iodine uptake. In conclusion, the efficacy of KI depends on the given amount and the time of ingestion.

In “real-life” conditions, KI has also been widely used after nuclear accidents as an ITB agent; the largest clinical experience reporting its use is the prophylaxis program undertaken by the Polish government after the Chernobyl accident, which included 12,084 children and 5,825 adults who took the KI prophylaxis treatment. Overall, no thyroid dysfunction has been observed in the studied population over a 10 years-follow-up period.

The systematic review found in literature suggests that KI intake following a nuclear accident may reduce the risk of developing thyroid cancer, particularly in children who have been exposed to radiation. However, these results need to be interpreted with caution since the quality of evidence is low. No conclusion could be drawn about the effectiveness of KI intake with respect to the prevention of hypothyroidism and benign thyroid nodules.

KI as ITB treatment is endorsed since 1999 by WHO’s Guidelines for Iodine Prophylaxis following Nuclear Accidents and is also widely implemented in most international and national guidelines [e.g., FDA 2001; EC 2010]. Those guidelines include the same recommendations concerning the dosing regimen and the timing of administration which are also reflected in the proposed product information for Kaliumjodid SERB 65 mg tablets.

In conclusion, although evidence for efficacy from state-of-the-art clinical trials are lacking, KI effectiveness from mechanistic and observational studies as well as from expert opinions is established which is also reflected in international and national guidelines from scientific bodies. KI is considered as the most effective preventive radiation management when administered in a timely appropriated manner and with an adequate dosage. The posology and the method (timing) of administration proposed in this application are in line with the latest reference guidelines recommendations.

Clinical safety

General safety profile

Safety profile of KI resemble to that of iodide / iodine-containing products. Adverse drug reactions (ADRs) related to the presence of iodine are well known and fully described:

- Iodine and iodides have variable effects on the thyroid and can produce hyperthyroidism as well as goitre and hypothyroidism; this should be considered especially in patients with history of evolutive thyroid disease and goitres.

- Hypersensitivity reactions to iodides are exceptional. Those may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.

- Large doses or prolonged use of iodides may lead to a range of adverse effects, often called `iodism', some of which resemble hypersensitivity reactions. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be coryza-like symptoms, and swelling and inflammation of the throat and salivary glands. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchospasm may develop. Skin reactions include mild acneiform eruptions or, more rarely, severe eruptions (iododerma). Other

reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances.

- Oral administration of iodine can also cause a metallic taste, thirst, and corrosive effects on the gastrointestinal tract; vomiting, abdominal pain, and bloody diarrhoea can occur.

- All iodide/iodine-containing products are contraindicated for two rare auto-immune conditions:
  - Dermatitis herpetiformis (Duhring-Brocq disease)
  - Hypocomplementemic urticarial vasculitis (Mac Duffie syndrome)

The presence of potassium in KI may add other safety concerns for this product, especially related to drug interactions. However, usual doses of KI used for radiation protection (i.e., up to 130 mg) contain low amounts of potassium compared to dietary adequate daily intakes for potassium (from 400 mg in infants up to 3,400 mg in adults) and should not be critical for the safety of this medicinal product.

Safety in special populations

Paediatric population
The consequences of radiation exposure of the thyroid gland are well known. The risk of thyroid carcinoma after exposure to doses higher than 0.05 - 0.1 Gy is higher in younger children at the time of exposure. As their thyroid gland is still growing, new-borns and children are more susceptible to the dangerous effects of radioactive iodide than adults and should be treated with KI in priority [WHO 2017]. Moreover, since iodine (whether stable or radioactive) readily crosses the placenta and considering that foetuses begin concentrating iodine and synthesizing thyroid hormones after 12 weeks of gestation, foetuses older than 12 weeks are also at high risk of radiation exposure [WHO 2017].

Neonates (birth to 1 month of age) given KI should be monitored for the potential development of hypothyroidism by measuring thyrotropin (thyroid-stimulating hormone, TSH) and, if indicated, free thyroxine (free T4) and thyroid replacement therapy should be instituted if hypothyroidism occurs. In addition, repeated administration of KI should be avoided in neonates to minimize the risk of hypothyroidism during a period of critical brain development.

Pregnancy
KI intake during pregnancy may result in abnormal thyroid function and/or goitre in the neonate. If KI is used during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be informed of the potential risks to the foetus.

No dosage adjustments are required during pregnancy [WHO 2017]. However, pregnant women should not receive repeated administration of KI [FDA 2001; EC 2010; WHO 1999; WHO 2017].

Breast-feeding
Lactating females should be administered KI for their own protection and to potentially to reduce the radioiodine content of the breast milk [FDA 2001].

No dosage adjustments are required in breastfeeding women [WHO 2017]. However, breastfeeding women should not receive repeated administration of KI [FDA 2001; EC 2010; WHO 1999; WHO 2017].

Fertility
No data is available on KI effect on fertility in human.

Elderly population / Renal impairment / Hepatic impairment
Since older adults (over 60 years) are at higher risk of adverse health effects of stable iodine, this population should not receive repeated administration of KI [FDA 2001; EC 2010; WHO 1999; WHO 2017]. Because it becomes easier for the ingredients of administered drugs to remain in the body due

to decrease in liver detoxification and renal excretion, elderly people should be encouraged to consult a physician before taking iodine.

Subjects aged >40 years are more likely to have thyroid disease and therefore are at higher risk of developing thyroid related side effects with repeated adminstration [EC 2010; WHO 1999; WHO 2017]. Furthermore, the risk of radiation induced thyroid cancer is low in this population. Therefore, repeated dose of KI are not recommended in this population.

Iodine should be administered with caution in the case that the person exhibits renal dysfunction.

Safety data retrieved from literature

Early toxicity data of KI was collected in the study that investigated the basal thyroid uptake of radioactive iodine I-131 in healthy volunteers. Toxicity was negligible for this single administration, only two subjects reported adverse reaction with KI. Both experienced discomfort at the angles of the jaws when taking 1,000 mg of KI. Since 100 to 200 mg of potassium iodide was just as effective as 1,000 mg in causing uptake blockade and had the advantage of not eliciting undesirable side effects, the use of larger doses was deemed unnecessary.

The survey study describing the outcomes of KI treatment during the polish prophylaxis program after the Chernobyl accident in 1986 is the largest clinical experience with KI in the context of this application (including more than 12,000 children and 5,000 adults treated). This study has revealed the occurrence of digestive disorders (vomiting, diarrhoea, gastric pain) in 0.12 to 2.38% of cases, and minor skin rash in approximately 1% of cases. Four (4) cases of thyroid pain were reported in adults, and 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 KI prophylaxis. Twelve (12) (0.37%) out of 3,214 new-borns who received KI prophylaxis on the second day of life, showed a transient increase in serum TSH and decreased free serum thyroxine, remaining without known sequelae up to 1993. In patients with thyroid disease diagnosed and/or treated before 1986, clinical course was identical irrespective of iodide prophylaxis intake. In patients with nodular goitre, no case of thyrotoxicosis induction, exacerbation of pre-existing hyperthyroidism, change in antibody titres, or change of Graves' disease prevalence were observed. Overall, 4% (corresponding to 0.2% of the population studied) of all adverse reactions were considered medically significant.

A review investigated the adverse reactions to KI administration to block the thyroid, based on a systematic literature search in scientific medical databases. The search resulted in 14 articles relevant to the topic, reporting mostly on surveys, ecological and intervention studies. Only one study focused on effects (both desired and adverse) of an ITB intervention following the Chernobyl accident. All other studies reported on iodine administration in a different context. Overall, the studies did not reveal severe adverse reactions to KI in the general population. However, since ITB is a protective measure only applied in very specific circumstances, reporting of adverse effects are scarce and consequently the evidence base is weak. The evidence gathered in this review suggested that even the administration of comparatively high doses of KI did not result in serious adverse health outcomes in the exposed population groups. Severe reactions of clinical significance were rare and observed in individuals with pre-existing thyroid disorders and iodine sensitivity.

Post marketing data

No post-marketing data is available with Kaliumjodid SERB 65 mg tablets.

Actions taken by regulatory authorities for safety reasons

No action has ever been undertaken by regulatory authorities for safety reasons with Kaliumjodid SERB 65 mg tablets.

MPA conclusion on potassium iodide safety profile

The safety profile of KI is well known, similar to that of iodide and iodine-containing medicinal products. No new safety concerns have emerged from the literature. The use of KI in the context of ITB treatment in case of nuclear accident has not changed over the time.

In the context of the targeted indication, the large experience from the Polish prophylaxis program has principally revealed the occurrence of non-serious ADRs. Those were mostly digestive disorders (vomiting, diarrhoea and gastric pain) in 0.12 to 2.38% of cases, and minor skin rashes in approximately 1% of cases. Those ADRs are well-known and listed in the product information. The presence of potassium in KI may add an additional safety concern for this product, especially related to drug interactions. However, usual doses of KI used for radiation protection contain low amounts of potassium compared to dietary adequate daily intakes for potassium and should not be critical for the safety of this medicinal product.

The SmPC adequately reflects the safety profile of KI when used in the indication "*prophylaxis of radioactive iodine absorption on the thyroid gland in case of nuclear accident*".

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Kaliumjodid SERB.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.2 signed 29 April 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Kaliumjodid RECIP 65 mg tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Importance of favourable and unfavourable effects

Although evidence for efficacy from state-of-the-art clinical trials are lacking, KI effectiveness in blocking thyroid uptake of radioactive iodine from mechanistic and observational studies is established, which is also reflected in international and national guidelines from scientific bodies. KI is considered as the most effective preventive radiation management when administered in a timely appropriated manner and with an adequate dosage. The posology and the method (timing) of administration proposed in this application are in line with the latest reference guidelines recommendations.

The safety profile of KI is well known, similar to that of iodide and iodine-containing medicinal products. No new safety concerns have emerged from the literature. The use of KI in the context of ITB treatment in case of nuclear accident has not changed over the time.

Balance of benefits and risks

High rates of thyroid tumours have been observed in contaminated areas following the release of large amounts of radioactive iodine in nuclear accidents. Radioactive iodine uptake by the thyroid can be effectively blocked by a single, high and timely appropriate dose administration of stable iodine. Foetuses, infants, children, pregnant women and nursing mothers are most in need of protection from radioiodine exposure since they have the highest risk of cancer.

Regarding the risks, the safety profile of KI is well known, similar to that of iodide and iodine containing products. Usual doses of KI used for radiation protection have an acceptable safety profile.

Conclusions

The benefit-risk balance of Kaliumjodid SERB in prophylaxis against effects of radioactive iodine on the thyroid gland in case of a nuclear accident, remains positive.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Kaliumjodid SERB, 65 mg, tablet was positively finalised on 2022-09-20.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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