1. NAME OF THE MEDICINAL PRODUCT

Irenat drops 300 mg/ml oral drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution (about 15 drops) contains 344.2 mg of sodium perchlorate 1 H_2O (equivalent to 300 mg of sodium perchlorate)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral drops

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

For the treatment of hyperthyroidism, to block the thyroid gland in scintigraphic examinations of other organs with radioactively-labelled iodine or immune scintigraphies for tumour location with radioactive iodine labelled antibodies. For the detection of a congenital iodine organification defect (perchlorate discharge test).

4.2 Posology and method of administration

Posology

Adults receive a loading dose in the first 1-2 weeks of 4-5 x 10 Irenat drops daily (corresponding to 800-1000 mg sodium perchlorate), in exceptional cases, 5 x 15 Irenat drops daily (corresponding to 1500 mg sodium perchlorate). The average maintenance dose is 4 x 5 Irenat drops (equivalent to 400 mg sodium perchlorate) per day.

Children aged 6-14 years are treated with a continuous dose of 3-6 x 1 or 4-6 x 2 drops of Irenat daily (corresponding to 60-240 mg sodium perchlorate).

When used for so-called perchlorate discharge test after administration of the radioactive iodine tracer dose a single dose of Irenat 30-50 drops (corresponding to 600-1000 mg sodium perchlorate) is administered; in children of 300 mg -600 mg/m^2 body surface is administered.

For pretreatment in scintigraphic studies which do not affect the thyroid gland itself and where iodine- or technetium-containing, radioactively-labelled drugs or antibodies are used, Irenat drops in doses of 10 - 20 drops (equivalent to 200-400 mg of sodium perchlorate) are administered to reduce the radiation dose to the thyroid gland and for blocking the radionuclide uptake in certain compartments, in individual cases up to 50 drops (equivalent to 1000 mg of sodium perchlorate).

Method of administration

Because of possible gastrointestinal side effects, Irenat drops should be taken with plenty of water, preferably after a meal and, because of the short duration of action, in 4-6 individual doses spread over the day.

The duration of treatment is dependent on the indication and depends on the clinical picture and the accompanying therapy function tests.

If after 2 years of thyrostatic therapy no remission has occurred or there is already a hyperthyreose recidivity, (strumectomy/radioiodine therapy) other age-appropriate treatment options should be considered.

To block the thyroid before scintigraphy of other organs (e.g. brain imaging) and where radioactively-labelled iodine or technetium is used as a tracer, the daily intake of Irenat drops four days before and, because of the rebound phenomenon, 2 to 3 weeks after application of the nuclide is recommended in combination with thiourea derivatives for reducing the radiation dose to the thyroid gland.

4.3 Contraindications

Irenat drops should not be taken for:
- substernal goitre,
- hypersensitivity to perchlorates or to any of the excipients listed in section 6.1,
- in the case of preexisting blood dyscrasias occurring with perchlorate administration, particularly
- agranulocytosis,
- during Plummer's treatment while preparing for surgery.

4.4 Special warnings and precautions for use

During antithyroid therapy regular and frequent monitoring of thyroid function is necessary to adjust the dosages of Irenat drops to the current metabolic status and to avoid over-treatment which may lead to goitre and hypothyroidism symptoms. The risk of the negative effects of an inadequately high dose is great, especially in intrathoracic goitre. All patients should be advised of the need for regular blood tests.
Through interference with the electrolyte electrode of blood gas analysers erroneously low concentrations of ionized calcium can be measured when using Irenat drops.

Severe skin reactions
Cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Irenat. Patients should be informed of the signs or symptoms of these severe reactions and be closely monitored for signs or symptoms of SJS and TEN (such as progressive skin rash, often with blisters or accompanying mucosal lesion). Treatment should be discontinued immediately at the first appearance of skin and/or mucosal reactions (see section 4.8). If the patient has developed SJS or TEN, treatment with Irenat must not be restarted at any time.

4.5 Interaction with other medicinal products and other forms of interaction

The radioactive iodine or ^{99m}Tc pertechnetate uptake is dose-dependently inhibited by perchlorate. TSH stimulation of radioactive iodine uptake is not affected by perchlorate.

In simultaneous administration of perchlorate and propylthiouracil or thiamazole respective carbimazole for antithyroid therapy, the antithyroid effect will be amplified, because of the different points of attack of sodium perchlorate and the thiourea derivatives.

Simultaneous thiamazole addition led to a positive perchlorate discharge test (even in hyperthyroid and healthy subjects) by inhibiting iodine organification.

A simultaneous iodine administration (for example, iodine-containing drugs or X-ray contrast agents, perioperative Plummer syndrome) reduces the effect of Irenat drops.

4.6 Fertility, pregnancy and lactation

Pregnancy
Irenat drops should not be used during pregnancy because of lack of experience of the potential risk to the foetus. Irenat drops pass freely across the placenta to the foetus. The foetal thyroid is possibly more sensitive to anti-thyroid drugs than the adult thyroid.

Lactation
Studies on the excretion of sodium perchlorate in breast milk are not available. If during lactation therapy with Irenat drops is required, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

In the evaluation of side effects following frequencies are defined as

Common	(≥ 1% to <10%)
Uncommon	(≥ 0.1% to <1%)
Rare	(≥ 0.01% to <0.1%)
Very rare	(< 0.01% or unknown)

The occurrence of side effects are dose-dependent.

Common (≥ 1% to <10%)
- A fleeting rash,
- Nausea or vomiting,
- Dry mouth, pharyngitic irritation,
- Lymphadenopathy,
- Leukopoenia,
- Purpura,
- Febrile arthralgia,
- Drug fever.

Uncommon (≥ 0.1% and <1%)
- Initial diarrhoea,
- Slight muscle cramps,
- Burning in the feet,
- Heaviness in the head,
- Eosinophilia,
- Itching,
- Jaundice.

Occasionally, it can lead to agranulocytosis, which usually regresses rapidly and without consequences after discontinuation of Irenat drops.

Very rare (< 0.01%)
- Agranulocytosis with fatal consequences,
- Thrombocytopoenia or aplastic anaemia with fatal outcome (incidence of approximately 0.1%),
- Minimal albuminuria,
- Nephrotic syndrome, partially or fully reversible,
- Hair loss,
- Acne,

- Generalised dermatitis,
- Urticaria,
- Liver damage with acute liver failure,
- Erythema nodosum with fever, antinuclear and antierythrocyte antibodies and eosinophilia,
- Perforation of a duodenal ulcer.

Not known (cannot be estimated from the available data)
- Severe skin reactions such as Stevens Johnson Syndrome, toxic epidermal necrolysis (see section 4.4)

In most cases, these extremely rare mutations were observed under an ongoing perchlorate medication without proof of a causal link.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Website: www.bfarm.de

4.9 Overdose

Taking the Irenat drops undiluted may, for example, in children, exercise a strong local irritant effect with symptoms such as vomiting, abdominal pain and diarrhoea.

Acute fatal poisoning with perchlorates is not known. Sodium perchlorate is tolerated in amounts up to several grams. The value of detoxifying measures, such as gastric lavage and forced diuresis inter alia, is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: thyroid therapeutic/thyreostatic drug, ATC code: H03BC

Perchlorate competitively inhibits the iodine uptake mechanism of the thyroid gland, the iodination, and affects iodisation by washing out accumulating iodide, not yet incorporated in the thyroglobulin molecule, from the thyroid gland.

The extrathyreoidal reutilisation of the iodide released in the deiodination of the thyroid hormone is also inhibited.

Similarly, the uptake of iodide split off during administration of iodine-containing contrast agents can be competitively inhibited by perchlorate. The same applies to the technetium pertechnetate uptake.

Perchlorate generally produces its effect anywhere, as in the thyroid, where there is an active iodine transport mechanism (e.g., in the salivary glands) and renal iodide excretion is also increased.

The thyreostatic effect is based on the iodine impoverishment brought about.

5.2 Pharmacokinetic properties

The absorption of perchlorate occurs within a few minutes. The onset of action on the thyroid cell is very rapid after oral administration. The iodine uptake blocking after a single dose only lasts for a few hours; in hyperthyroidism it is shortened, so that daily repeated doses are required to maintain effective serum levels constant.

In administration accompanying scintigraphy, the blocking of the radionuclide uptake lasts until the subsequent decay of the perchlorate-serum level.

The half-life of the perchlorate in humans is not known exactly. Maximum tissue levels in the thyroid gland are reached after 4 hours.

Perchlorate is bound to albumin. There can be no in vivo metabolism and it is excreted rapidly and almost completely unchanged by the kidneys. >95% is eliminated after 72 hours.

5.3 Preclinical safety data

a) Acute toxicity
In humans, 1 or 2 g per os showed no toxic effects.

The intravenous injection of 250 mg sodium perchlorate in rabbits had no toxic effects. However, the intracardiac injection of 500 mg produced a temporary paralysis of the hind legs.

b) Chronic Toxicity
Doses of 250 mg/kg body weight over 40 weeks did not produce any toxic side effects in animal experiments. In the mouse, dose-dependent toxic effects such as paralysis, skeletal changes, proptosis, reduction reaction, and hair loss were described at a dose of 1460 mg/kg of body weight.

c) Mutagenic and tumorigenic
Mutagenicity investigations are not available for sodium perchlorate.

In rats, the extrathyroidal tumour rate was below the long-term intermittent treatment with high perchlorate doses in the range of the expected spontaneous tumour rate.

Polymorphic changes in breast and thyroid are described, but the bounds for malignant changes were not exceeded in animal studies.

d) Reproductive toxicology
There are no adequate studies in animals to be able to rule out a possible embryo/foetotoxic effect of sodium perchlorate.

In the rat neither the implant nor the survival of the embryo until day 13 p. c. was impaired by the oral administration of a 1% potassium perchlorate solution.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium chloride, magnesium chloride, calcium chloride, purified water

6.2 Incompatibilities

None known

Other information
Irenat drops should be discontinued at least 3 days before making a thyroid or radionuclide uptake measurement.

For use during pregnancy and lactation, see section 4.6.

6.3 Shelf life

The shelf life is 4 years. After opening the bottle do not use after 26 weeks at room temperature.

This drug should not be used after the expiration date.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Irenat drops are available in a bottle containing 40 ml of solution.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharma (Ireland) Ltd
United Drug House
Magna Drive
Dublin
D24 X0CT
Irland

8 MARKETING AUTHORISATION NUMBER

6044463.00.00

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09.10.1996
Date of last renewal: 22.05.2013

10 DATE OF REVISION OF THE TEXT

01/2019

11 CLASSIFICATION

ADDITIONAL INFORMATION (national characteristics)

	Information	Information changed compared to the previous (x = yes!)
	MAH	x
Version	DE10	x
Date of information	January 2019	x