LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2016-02-15

# Public Assessment Report
# Scientific discussion

# Iberogast, oral drops solution

**(*Iberis amara* L., planta tota recens, liquid extract (1:1.5-2.5), ethanol 50 %**
***Angelica archangelica* L., radix, liquid extract (1:2.5-3.5), ethanol 30 %**
***Matricaria recutita* L., flos, liquid extract (1:2-4), ethanol 30 %**
***Carum carvi* L., fructus, liquid extract (1:2.5-3.5), ethanol 30 %**
***Silybum marianum* (L.) Gaertn., fructus, liquid extract (1:2.5-3.5), ethanol 30 %**
***Melissa officinalis* L., folium, liquid extract (1:2.5-3.5), ethanol 30 %**
***Mentha piperita* L., folium, liquid extract (1:2.5-3.5), ethanol 30 %**
***Chelidonium majus* L., herba, liquid extract (1:2.5-3.5), ethanol 30 %**
***Glycyrrhiza glabra*, L., radix, liquid extract (1:2.5-3.5), ethanol 30 %)**

# Asp no: 2008-1483

**This module reflects the scientific discussion for the approval of Iberogast, oral drops solution. The procedure was finalised 10 November 2010. For information on changes after this date please refer to the module 'Update'.**

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# LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted a marketing authorisation for the herbal medicinal product Iberogast, oral drops, solution. The product is available without prescription and can be bought from pharmacies only.

Iberogast is approved with the following indication: Herbal medicinal product for relief of symptoms of functional dyspepsia and IBS, such as the gripes, pain or a burning sensation in the epigastrium, bloating and nausea.

The active ingredients are extracts from:

- *Iberis amara*, fresh whole plant (bitter candytuft, blomsteriberis)
- *Angelica archangelica*, dried root (angelica, kvanne)
- *Matricaria recutita*, dried flower (matricaria, kamomill)
- *Carum carvi*, dried fruit (caraway, kummin)
- *Silybum marianum*, dried fruit (milk thistle, mariatistel)
- *Melissa officinalis*, dried leaves (melissa, citronmeliss)
- *Mentha piperita*, dried leaves (peppermint, pepparmynta)
- *Chelidonium majus*, dried herb (greater celandine, skelört)
- *Glycyrrhiza glabra*, dried root (liquorice, lakritsrot)

The Medical Products Agency has concluded that the active substances in Iberogast have a recognised efficacy and acceptable level of safety in the approved indication.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Iberogast could be granted a marketing authorisation as a herbal medicinal product.

# I. INTRODUCTION

Green Medicine AB has applied for a marketing authorisation for Iberogast, oral drops, solution. The application was submitted under Article 8(3), Known active substance, of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substances are:

- *Iberis amara* L., planta tota recens, liquid extract (1:1.5-2.5), ethanol 50 %
- *Angelica archangelica* L., radix, liquid extract (1:2.5-3.5), ethanol 30 %
- *Matricaria recutita* L., flos, liquid extract (1:2-4), ethanol 30 %
- *Carum carvi* L., fructus, liquid extract (1:2.5-3.5), ethanol 30 %
- *Silybum marianum* (L.) Gaertn., fructus, liquid extract (1:2.5-3.5), ethanol 30 %
- *Melissa officinalis* L., folium, liquid extract (1:2.5-3.5), ethanol 30 %
- *Mentha piperita* L., folium, liquid extract (1:2.5-3.5), ethanol 30 %
- *Chelidonium majus* L., herba, liquid extract (1:2.5-3.5), ethanol 30 %
- *Glycyrrhiza glabra* L., radix, liquid extract (1:2.5-3.5), ethanol 30 %

For approved indications, see the Summary of Product Characteristics (SmPC).

# II. QUALITY ASPECTS

## II.1 Introduction

Iberogast is presented in the form of oral drops, solution. 1 ml of the solution contains:

- 0.15 ml liquid extract* of *Iberis amara* L., planta tota, corresponding to 60-100 mg fresh whole plant.
- 0.10 ml liquid extract** of *Angelica archangelica* L., radix, corresponding to 30-40 mg dried root.
- 0.20 ml liquid extract** of *Matricaria recutita* L., flos, corresponding to 50-100 mg dried flower.
- 0.10 ml liquid extract** of *Carum carvi* L., fructus, corresponding to 30-40 mg dried fruit.
- 0.10 ml liquid extract** of *Silybum marianum* (L.) Gaertn., fructus, corresponding to 30-40 mg dried fruit.
- 0.10 ml liquid extract** of *Melissa officinalis* L., folium, corresponding to 30-40 mg dried leaves.
- 0.05 ml liquid extract** of *Mentha piperita* L., folium, corresponding to 10-20 mg dried leaves.
- 0.10 ml liquid extract** of *Chelidonium majus* L., herba, corresponding to 30-40 mg dried herb.
- 0.10 ml liquid extract** of *Glycyrrhiza glabra* L., radix, corresponding to 30-40 mg dried root.

* Extraction solvent: ethanol 50 % V/V
** Extraction solvent: ethanol 30 % V/V

The product contains no excipients except for the extraction solvents.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise and Good Agricultural and Collection Practice, respectively).

### II.2 Drug Substance

All herbal substances comply with their respective monographs in the European Pharmacopoeia (Ph. Eur.), except for *Iberis amara* which complies with a monograph in the German Drug Codex (DAC). Additional tests such as residues of heavy metals, pesticides, aflatoxins and microbiological quality comply with the general monograph for herbal drugs.

The plants used are mainly cultivated in Europe but also in North America, Asia, Egypt and Europe as well as collected from the wild in Asia and Europe. Relevant information on growing conditions and controls of the herbal substance (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials (herbal substance) and solvents. The tests and limits in the specifications are considered appropriate to control the quality in relation to the intended purpose.

The specifications of the active substances (herbal preparations) include relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted.

### II.3 Medicinal Product

Iberogast, oral drops, solution are formulated without using any excipients except for the extraction solvents.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

## III. NON-CLINICAL ASPECTS

### III.1 Introduction

The applicant has collected information from the literature and has performed extensive product-specific studies covering many areas of non-clinical pharmacology and toxicology.

## III.2 Pharmacology

Binding to serotonin receptors was shown for STW 5 SE (STW 5 SE is the name of the extract constituting the active substance in Iberogast) and for the individual crude drugs *Chelidonium majus* herba, *Matricaria recutita* flos, and to a lesser extent *Iberis amara* herba recens, *Mentha piperita* folium and *Angelica silvestris* radix. Binding to muscarine $M_3$ receptors was demonstrated for STW 5 SE and for the individual drugs *Chelidonium majus* herba, *Iberis amara* herba recens, and *Angelica archangelica* radix.

Inhibition of acid production, as demonstrated with isolated and enriched guinea pig parietal cells, has been shown for STW 5 SE and for the individual crude drugs *Iberis amara* herba recens, *Matricaria recutita* flos, *Mentha piperita* folium, *Chelidonium majus* herba and *Glycyrrhiza glabra* radix.

STW 5 SE relaxes isolated stomach wall strips from the regions corpus and fundus in the guinea pig. On the antrum region an increase in phasic activity was demonstrated. The individual crude drugs had different activities on the motility of the stomach wall regions. *Iberis amara* herba recens increased the tonic and phasic activity in all three regions, whereas *Chelidonium majus* herba had an increasing effect only in the antrum region. *Angelica archangelica* radix had a relaxing effect in the fundus area.

STW 5 SE acts tonicising on relaxed ileum and relaxing on contracted ileum. Anti-ulcerogenic effect measured as effects on prostaglandin E2 and leukotriene levels in the gastric mucosa has been demonstrated for STW 5 SE and for *Iberis amara* herba recens, *Carum carvi* fructus, *Angelica archangelica* radix, *Mentha piperita* folium, *Glycyrrhiza glabra* radix and *Matricaria recutita* flos.

Antibacterial activity on *Helicobacter pylori* was exerted by STW 5SE. *Angelica archangelica* radix, *Chelidonium majus* herba, *Matricaria recutita* flos, *Mentha piperita* folium, *Melissa officinalis* folium and *Glycyrrhiza glabra* radix all contributed to this effect.

It has been shown that each of the 9 crude drugs contained in STW 5 SE is of importance for the overall effect. The results from the product-specific studies are supported by information from handbooks.

## III.3 Pharmacokinetics

Very little information on the actual extracts in STW 5SE is available.
Only an *in vitro*-absorption study has been performed which showed that carvone, as an example for strongly non-polar substances and rosmarinic acid, as an example for strongly polar substances were absorbed from STW 5 SE at rates comparable to those from extracts of *Carum carvi* fruits and rosmarinic acid from extracts of *Melissa officinalis* leaves. In connection with toxicity studies it was shown that glycyrrhizin, as a marker substance, was well absorbed from STW 5 SE in rats, rabbits and beagle dogs.

## III.4 Toxicology

Product-specific investigations of single-dose and repeat-dose toxicity have shown a very low toxicity for STW 5 SE.
*In vivo* genotoxicity studies on the product-specific extract have been performed. No genotoxicity could be found for STW 5 SE in the tests performed. Nor are there any reports in the literature of genotoxicity for the individual crude drugs.

Studies of reproductive and development toxicity have been performed on STW 5 SE. The results were negative. The literature contains no reports on reproductive and development toxicity for the individual crude drugs.

One of the constituents in STW 5SE, *Iberis amara* herba recens contains the toxic compounds cucurbitacins E and I. A cytotoxicity study in V 79 cells for the *Iberis amara* extract gives support for a low toxic potential and the safety margin appears to be sufficient. *Chelidonium majus* extract contains small amounts of alkaloids for which hepatotoxic effects have been discussed. A cytotoxicity study in human hepatocytes supports the conclusion from the *in vivo* toxicology studies that STW 5 SE does not have hepatotoxic effects, at least at doses up to 1000 mg/kg bw/day (600 times the recommended dose).

Due to the fact that some furocoumarins possess phototoxic effects, the applicant was asked to present a risk assessment of the total content of furocoumarins from *Angelica archangelica* radix in STW 5 SE in accordance with the HMPC reflection paper (EMEA/HMPC/317913/2006). The answer is satisfactory and the issue concerning phototoxic and photogenotoxic risks has been adequately assessed.

In summary, available non-clinical information constitutes no cause for safety concern.

### III.5 Ecotoxicity/environmental risk assessment

Iberogast is a herbal medicinal product. According to *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SW4447/00), herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

### III.6 Discussion on the non-clinical aspects

The available non-clinical information constitutes no cause for safety concern. The inactive ingredients in Iberogast do not constitute any safety concern. None of the ingredients in Iberogast are of animal origin.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

The documentation contains an extensive review of the medical literature (handbooks etc.) pertaining to herbal substances included in Iberogast. They all have longstanding uses in herbal medicinal products for the relief of dyspeptic gastrointestinal symptoms like minor spasms, epigastric pain and distension etc. This does not in itself constitute a proof of clinical efficacy, but establishes that the ingredients in Iberogast *de facto* have been used in this way for a long time (at least decades).

The currently approved indication for Iberogast reads: Herbal medicinal product for relief of symptoms of functional dyspepsia and IBS, such as the gripes, pain or a burning sensation in the epigastrium, bloating and nausea.

### IV.2 Pharmacokinetics

No information available.

## IV.3 Pharmacodynamics

The exact mechanism of action is not known.
A clinical pharmacological study (Pilichiewicz et al., (2007) Effects of Iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. Am J Gastroenterol. Jun; 102(6):1276-83.) has been performed on the effects of Iberogast and oral control (30.9 % ethanol), each administered as a single dose (1.1 ml), in a double-blind randomized fashion, on proximal gastric volume (part A), antropyloroduodenal motility (part B), and gastric emptying and intragastric distribution of a solid/liquid meal (part C) for 120 minutes, in 9 (part A), 12 (part B), and 8 (part C) healthy men.

Results: Iberogast increased proximal gastric volume (max volume; Iberogast 174 ± 23 mL, control 104 ± 12 mL ($P < 0.05$) (part A), increased the motility index of antral pressure waves in the first 60 minutes compared to control ($P < 0.05$) without affecting pyloric or duodenal pressures (part B), and slightly increased the retention of liquid in the total stomach between 10 and 50 minutes compared to control ($P < 0.01$), but had no effect on gastric emptying of solids (part C).

Conclusions: Iberogast affects gastric motility in humans, in a region-dependent manner, by relaxing the proximal stomach and stimulating antral motility.

## IV.4 Clinical efficacy

The documentation contains the results of 4 pivotal clinical studies in patients diagnosed with functional dyspepsia (FD).

**Main study 1** (v. Arnim et al (2007), STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. Am J Gastroenterol. Jun; 102(6): 1268-75) was a multicenter, double-blind, randomized, placebo-controlled study, performed in accordance with GCP. 315 patients (157 Iberogast; 158 placebo) received 3 x 20 drops of study medication for a period of 8 weeks.

The primary efficacy parameter was the change in the sum score of the validated scale GIS (gastrointestinal symptoms profile) filled in by the investigator. The GIS comprises 10 dyspeptic symptoms: epigastric pain/upper abdominal pain, abdominal cramps, fullness, early satiety, loss of appetite, sickness, nausea, vomiting, retrosternal discomfort, and acidic regurgitation/heartburn. Symptom severity was assessed by a validated 5-point Likert scale: none (0), slight (1), moderate (2), severe (3), and very severe (4). The score is used for the outcome measurement as a sum score, with its highest value of 40 points representing the most severe symptom intensity.

The secondary target variables comprised the overall efficacy and tolerability of the 8-wk treatment with Iberogast or the placebo, assessed by investigator and patient using a 6-point Likert scale ranging from very good (1) to very poor (6). On the GIS scale, the treatment difference between the Iberogast group and the placebo group in the ITT population was 1.04 (p=0.0407). In the PP population, the GIS difference was 1.77 points (p=0.0022) in favour of the Iberogast group. One score point in the GIS is considered the minimum clinically relevant difference perceived by the patient. The global rating of efficacy by the patient and investigator showed significant advantages for Iberogast (p=0.0399 and p=0.0207; exact Wilcoxon-Mann-Whitney test over all six response categories). Roughly twice as many investigator ratings confirmed a "very good" effect of Iberogast compared to placebo (20.6 % versus 10.8 %; patient rating: 17.7 % versus 10.8 %

**Main study 2** (Braden, B. et al. (2009), Clinical effects of STW 5 (Iberogast®) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. Neurogastroenterology & Motility, 21: 632–e25.) was a double-blind, randomised, multicenter study (GCP) to compare efficacy and safety of Iberogast versus placebo (both given 3 x 20 dr daily) in functional dyspepsia with respect to gastric emptying. 93 patients (48 Iberogast; 45 placebo) entered the trial.

The primary target criterion was the change of the gastrointestinal symptoms profile (GIS) score, from baseline (Day 0) to end of study (Day 28) (Iberogast versus placebo).
Iberogast and placebo improved functional dyspepsia. Compared to placebo, a trend towards a difference in favour of Iberogast was observed in the ITT population. The outcome of the primary efficacy variable for the Iberogast group was not significantly different from that of the placebo group, when tested according to the statistical method described in the trial protocol. The outcome of the trial must thus be noted as negative for Iberogast. According to the calculations in the study protocol, at least 54 patients were required for each group. This number of patients was not enrolled in the study.

**Main study 3** (Madisch et al. (2001), A plant extract and its modified preparation in functional dyspepsia. Results of a double-blind placebo controlled comparative study]. Z Gastroenterol. 2001 Jul; 39(7): 511-7.) was a randomised, placebo-controlled, double-blind pilot study in four gastroenterological centres. 20 patients received Iberogast and 20 patients received placebo.

The main study variable was the change in the Gastrointestinal Symptom Profile (GIS) sum score in the total collective (intent-to-treat analysis).
Starting with similar baseline values, the GIS under the treatment with Iberogast was significantly lower than under the placebo treatment ($p < 0.001$), both after 14 days and after 28 days. The trial is very small in size.

**Main study 4** (Hachmann 1992; Buchert 1994) was a multicenter, placebo-controlled, parallel comparative study of the efficacy and safety of Iberogast versus placebo. The study was carried out in accordance with GCP guidelines. 80 patients received Iberogast and 73 received placebo (3x 20 dr daily for 4 weeks).

The summary score of the GIS was reduced in the Iberogast group from Week 0: 15.9 to Week 4: 6.8 and in the placebo group from Week 0: 16.5 to Week 4: 12.6 ($p<0.0001$).
The summary score of the pain intensity was reduced in the Iberogast group from Week 0: 5.6 to Week 4: 2.5 and in the placebo group from Week 0: 5.8 to Week 4: 4.4 ($p<0.0001$).
Albeit not a very large study, the results clearly indicate that the efficacy of Iberogast is significantly higher than placebo in reducing the symptoms of dyspepsia ($p<0.001$) on GIS score. The pain related symptoms of the GIS have been analysed in a subgroup and they were also reduced significantly better under Iberogast than under placebo ($p<0.001$).

In addition to the four trials in functional dyspepsia, the results of one trial (GCP) in patients with IBS have been submitted (**Main study 5**; Madisch A, Holtmann G, Plein K, Hotz J. (2004), Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. Aliment Pharmacol Ther. 2004 Feb 1; 19(3): 271-9) in which 51 patients were treated with Iberogast and 52 patients were treated with placebo (3x20dr daily for 28 days).

The primary study variable was the improvement in the symptoms of irritable colon under the treatment with Iberogast compared to a placebo determined on the basis of the pain profile

sum score and the abdominal symptom profile sum score. The course of the symptoms of irritable colon was documented by means of questionnaires (pain profile, abdominal symptom profile).

Under Iberogast a significantly higher improvement was observed for both study variables and a small improvement in the symptoms and the pain was observed in the placebo group. The decrease in the pain profile sum score was 3.7 ± 2.8 for Iberogast compared to 2.3 ± 2.7 for placebo (p=0.0148). The improvement in the abdominal symptom profile sum score was 3.1 ± 2.1 for Iberogast and 1.9 ± 1.6 for placebo (p=0.0032).

In summary, Iberogast has shown a statistically significantly better effect than placebo in 3 out of 4 clinical trials in FD. The size of the effect compared to placebo appears modest. In several of the studies, as secondary endpoints, the patients and investigators have been asked to give a global rating of the efficacy of the treatment, and here Iberogast has generally received higher ratings than placebo.

In 4 different meta-analyses of Main studies 1, 3 and 4 + 2 other clinical studies, it has been concluded that Iberogast is more effective than placebo in reducing the symptoms of FD. The fifth study dealt with irritable bowel syndrome (IBS) and indicated that Iberogast is more efficient than placebo in reducing the pain and abdominal symptom also of IBS (composite symptom scores). Most of these symptoms are seen in FD and the two disorders FD and IBS have been considered as different manifestations of the same type of disease.

## IV.5 Clinical safety

A comparison of the doses of the individual herbal substances contained in a daily dose of Iberogast with the doses recommended in Hager´s handbook shows that the daily intake of the individual herbal substances in Iberogast is much smaller than the doses used for the single preparations, which gives a good indication of the safety of the product.
The following table is a summary of patient exposures in clinical studies:

| Studies | Patients exposed |
|---|---|
| Placebo-controlled | 406 |
| Active –controlled | 99 |
| Open studies | 651 |
| Post marketing | 48 326 |

The adult dose was 20 drops x 3.
A total of 41 adverse events were reported from clinical studies and post-market surveillance. 19 of these were from the 5 main clinical studies reviewed above, 11 from the other clinical studies, 5 from open studies and 6 from post marketing surveillance. All events were mild (gastro-intestinal disturbances, short-term tiredness, and vegetative disorders). A causal relationship with Iberogast was judged as probable or possible. There were no deaths or other serious adverse drug reactions.

In addition to these events, 29 events have been reported from 1981 to 2007. These were also mild. 17 were allergic reactions. 1 case died, but relationship to study medication was classified as unlikely. The causality is also doubted in some of the other reports.
No clinically relevant pathological changes of the laboratory parameters have been reported.

In summary, no signals of clinical safety concern related to adverse effects of Iberogast can be identified in the documentation.

In conclusion, the clinical efficacy of Iberogast can be considered fairly well documented in clinical trials for symptomatic relief of functional dyspepsia. For the indication irritable bowel syndrome only one clinical study has been submitted, which indicated that Iberogast was better than placebo in reducing the pain and abdominal symptoms of IBS. The symptoms studied in this trial are very similar to the symptoms of FD, and in the scientific literature there is an ongoing discussion whether IBS and FD are slightly different manifestations of the same disease. It appears reasonable also to include symptomatic relief of IBS in the therapeutic indication for Iberogast.

Iberogast has been available as a medicinal product within The European Community for more than 45 years and in the submitted clinical safety documentation no signals of safety concern can be identified despite a very extensive clinical use.

## IV.6 Risk Management Plans

The MAH has submitted a risk management plan in the renewal process for Iberogast. This is the first RMP for Iberogast. The RMP has been assessed by the MPA and is 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 Iberogast.

Safety specification

*Summary table of safety concerns as approved in RMP*

| | |
|---|---|
| *Important identified risks* | *Hypersensitivity* |
| *Important potential risks* | *Treatment longer than one week without symptomatic improvement* |
| *Missing information* | *Use in children under 3 years* |

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 RMP is approved.

# V. PRODUCT INFORMATION

The product information (Summary of Product Characteristics, Package Leaflet and labelling) has been assessed and accepted by the Medical Products Agency.

User consultation

*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 language used for the purpose of user testing the PIL was German. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Iberogast, oral drops, solution is recommended for approval.

# VII. APPROVAL

Iberogast, oral drops, solution was approved in the national procedure on 2010-11-10.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2016-02-15

# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Change in MAH from Green Medicine to Bringwell Sverige AB | National | Y | 2012-12-07 | 2013-03-07 | Approval | N |
| Change in MAH from Bringwell Sverige AB to Bayer AB | National | Y | 2014-09-08 | 2014-12-01 | Approval | N |
| | | | | | | Y/N (version) |

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