SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
When marketed by Generics [UK] Limited as [POM] will be called Mebeverine 135 mg film-coated tablets

When marketed by Generics [UK] Limited as [P] will be called Mylan IBS Relief Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Mebeverine 135 mg film-coated tablets contain Mebeverine Hydrochloride BP 135 mg.

Excipient with known effect:
Each tablet contains 100 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

10 mm normal convex white film-coated tablets marked "MV135" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Mebeverine 135 mg film-coated tablets:
For the symptomatic treatment of irritable bowel syndrome and other conditions usually included in this grouping such as: chronic irritable colon, spastic constipation, mucous colitis, spastic colitis. Mebeverine is effectively used to treat the symptoms of these conditions such as: colicky abdominal pain and cramps, persistent, non-specific diarrhoea (with or without alternating constipation) and flatulence.

Mylan IBS Relief Tablets:
For the symptomatic relief of irritable bowel syndrome.
4.2 **Posology and method of administration**

**Mebeverine 135 mg film-coated tablets:**

For oral use.

**Posology**

The film-coated tablets should be swallowed with a sufficient amount of water (at least 100 ml water). They should not be chewed because of the unpleasant taste.

Duration of use is not limited.

If one or more doses are missed, the patient should continue with the next dose as prescribed; the missed dose(s) should not be taken in addition to the regular dose.

*Adults (including the elderly):*

One tablet three times a day, preferably 20 minutes before meals. After a period of several weeks, when the desired effect has been obtained, the dosage may be gradually reduced.

*Paediatric population:*

Mebeverine 135 mg film-coated tablets are not recommended for use in the paediatric population and adolescents below 18 years, due to insufficient data on safety and efficacy.

*Special population:*

No posology studies in elderly, renal and/or hepatic impaired patients have been performed. No specific risk for elderly, renal and/or hepatic impaired patients could be identified from available post-marketing data. No dosage adjustment is deemed necessary in elderly, renal and/or hepatic impaired patients.

**Mylan IBS Relief Tablets:**

For oral use.

**Posology**

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Duration of use is not limited.

If one or more doses are missed, the patient should continue with the next dose as prescribed; the missed dose(s) should not be taken in addition to the regular dose.

*Adults (including the elderly):*
One tablet three times a day, preferably 20 minutes before meals. If symptoms persist for more than 2 weeks, consult your doctor. Maximum daily dose of 405 mg.

Warning: Do not exceed the stated dose.

**Paediatric population:**
Mebeverine 135 mg tablets are not recommended for use in the paediatric population and adolescents below 18 years, due to insufficient data on safety and efficacy.

**Special population:**
No posology studies in elderly, renal and/or hepatic impaired patients have been performed. No specific risk for elderly, renal and/or hepatic impaired patients could be identified from available post-marketing data. No dosage adjustment is deemed necessary in elderly, renal and/or hepatic impaired patients.

### 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use
Since Mebeverine film-coated tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Mylan IBS Relief Tablets:**
The patient information leaflet used in the pharmacy pack will contain the following statements with regard to special precautions and warnings when taking Mebeverine.

If this is the first time you have had the symptoms described above, consult your doctor before using any treatment.

Please contact your doctor so that he can decide if Mylan IBS Relief Tablets is the right treatment for you if:

- you are aged 40 years or over
- you have passed blood from the bowel
- you are feeling sick or vomiting
- you have lost your appetite or lost weight
- you are looking pale and feeling tired
- you are suffering from severe constipation
- you have a fever
- you have recently travelled abroad
- you are, or may be, pregnant
- you have abnormal vaginal bleeding or discharge
- you have difficulty or pain passing urine

Consult your doctor if you have developed new symptoms, or if the symptoms worsen, or if they do not improve after 2 weeks of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed, except with alcohol. *In vitro* and *in vivo* studies in animals have demonstrated the absence of any interaction between mebeverine hydrochloride and ethanol.

4.6 Fertility, Pregnancy and lactation

**Pregnancy**

There are no or limited amounts of data from the use of mebeverine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Mebeverine is not recommended during pregnancy.

**Breastfeeding**

It is unknown whether mebeverine or its metabolites are excreted in human milk. The excretion of mebeverine in milk has not been studied in animals. Mebeverine should not be used during breast-feeding.

**Fertility**

There are no clinical data on male or female fertility; however, animal studies do not indicate harmful effects of mebeverine (see section 5.3).

4.7 Effects on ability to drive and use machines

No known studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic and pharmacokinetic profile as well as postmarketing experience do not indicate any harmful effect of mebeverine on the ability to drive or to use machines.

4.8 Undesirable effects

The following adverse reactions have been reported spontaneously during postmarketing use. A precise frequency cannot be estimated from available data.

Allergic reactions mainly but not exclusively limited to the skin have been reported.

**Immune system disorders:**
Hypersensitivity (anaphylactic reactions)

Skin and subcutaneous tissue disorders:
Urticaria, angioedema, face oedema and exanthema.

4.9 Overdose
On theoretical grounds it may be predicted that CNS excitability will occur in cases of overdose. In cases where mebeverine was taken in overdose, symptoms were either absent or mild and usually rapidly reversible. Observed symptoms of overdose were of a neurological and cardiovascular nature.

No specific antidote is known and symptomatic treatment is recommended.

Gastric lavage should only be considered in case of multiple intoxication or if discovered within about one hour. Absorption reducing measures are not necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Synthetic anticholinergics, esters with tertiary amino group

ATC code: A03A A04

Mebeverine is a β phenylethylamine derivative with strong papaverine like smooth muscle relaxant activity. It is a musculotropic spasmolytic drug with a strong and selective action on spasm of the smooth muscle of the gastrointestinal tract, particularly the colon, relieving spasm without affecting normal gut motility.

Mebeverine has a direct non-specific relaxant effect on vascular, cardiac and other smooth muscle. Studies indicate that the spasmolytic activity of mebeverine is not restricted to one particular system, but the compound possesses a polyvalent spasmolytic action in which at least three types of mechanisms are involved: A direct musculotropic action involving Ca^{2+} ion exchange and stabilisation of excitable membranes: A competitive anti-muscarinic activity of about 0.05-0.1 times that of atropine: A local anaesthetic activity together with potentiation of sympathetic inhibitory influences due to blockade of noradrenaline uptake into sympathetic nerve endings.

When tested in vivo in various species, mebeverine hydrochloride was found to be three to five times more powerful than papaverine in blocking spasm of smooth muscle and in relieving the carbachol-induced spasm of
the sphincter of oddi in rabbits, mebeverine hydrochloride proved to be twenty times more active than papaverine. **In vivo** studies also demonstrate that mebeverine has only minor effects on normal intestinal peristalsis but possesses spasmolytic activity when hypermotility is induced. The spasmolytic activity is found in all parts of the gastrointestinal tract and in some experiments has been found to be more active on colonic smooth muscle.

It is mainly used in the management of irritable bowel syndrome and other conditions usually indicated in this grouping such as irritable colon, spastic constipation, mucous colitis and spastic colitis. Mebeverine is effectively used to treat the symptoms of these conditions, such as ‘colicky’ abdominal pain and cramps, persistent, non-specific diarrhoea (with or without alternating constipation) and flatulence.

### 5.2 Pharmacokinetic properties

**Absorption:**
Mebeverine is rapidly and completely absorbed after oral administration of tablets.

Following oral administration of $^3$H and $^{14}$C labelled mebeverine hydrochloride in man, absorption was followed by the appearance in the plasma of veratric acid and an oxidised metabolite of the mebeverine alcohol moiety of the drug, mebeverine acid.

**Distribution:**
No significant accumulation occurs after multiple doses.

**Biotransformation:**
Mebeverine hydrochloride is mainly metabolised by esterases, which split the ester bonds into veratric acid and mebeverine alcohol firstly.

The main metabolite in plasma is DMAC (demethylated carboxylic acid).

The steady state elimination half-life of DMAC is 2.45 h. During multiple dosing $C_{max}$ of DMAC for the film-coated tablets with 135 mg is 1670 ng/ml and $t_{max}$ is 1 h.

Thus, the primary metabolic step in the mebeverine degradation is hydrolysis of the ester function. Maximum plasma radioactivity levels were found 1-3 hours after dosing. Binding of mebeverine to human serum albumin was 75%.

**Elimination:**
Mebeverine is not excreted as such, but metabolised completely; the metabolites are excreted nearly completely. Veratric acid is excreted into the urine, mebeverine alcohol is also excreted into the urine, partly as the corresponding carboxylic acid (MAC) and partly as the demethylated carboxylic acid (DMAC).
The major route of excretion of the metabolites is via the urine (95%) and the peak rate of excretion usually occurs within two hours. Virtually 98% urinary recovery of the conjugated and unconjugated metabolites was observed after a period of 24 hours. No unchanged mebeverine was excreted in the urine.

5.3 Preclinical safety data
During its development phase the entity mebeverine was extensively tested in several animal species in acute, (sub) chronic and reproduction investigations.

The oral LD$_{50}$ ranged from 902 - 1995 mg/kg.

The main symptoms in the animals, after very high oral and parenteral doses, were indicative of central nervous involvement with behavioural excitation.

The dosages used in animal studies exceeded several times the dosages used for humans (40 mg/kg for animal dosing versus 6 mg/kg for humans).

No mutagenic or clastogenic effects were found in in vitro and in vivo studies with mebeverine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mebeverine 135 mg film-coated tablets contain:

*Core tablet*
- Lactose monohydrate
- Cellulose, microcrystalline
- Povidone
- Sodium Starch Glycolate
- Talc
- Magnesium Stearate
- Water purified

*Film-coating*
- Opadry white Y-1-7000 containing the following;
  - Hydroxypropyl Methylcellulose (E464)
  - Titanium Dioxide (E171)
  - Polyethylene Glycol
6.2 **Incompatibilities**
None known.

6.3 **Shelf life**
5 years

6.4 **Special precautions for storage**
Store in a dry place, at a temperature not greater than 30°C. Protect from light.

6.5 **Nature and contents of container**
Polypropylene containers with polyethylene caps (with optional polyethylene ullage filler) and aluminium/PVdC blister packs.

Pack sizes: 12, 15, 18, 20, 21, 28, 30, 56, 60, 84, 90 and 100 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
There are no special instructions for the handling of Mebeverine 135 mg film-coated tablets.

7 **MARKETING AUTHORISATION HOLDER**
Milpharm
Ares Block
Odyssey Business Park
West End Road
Ruislip
HA4 6QD

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 16363/0470
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28 January 1997

10 DATE OF REVISION OF THE TEXT
26/01/2016