醣祿® 錠 50毫克，100毫克
Glucobay® Tablets 50mg, 100mg

α-Glucosidase抑制劑　　口服錠劑

衛署藥輸字第020786號
衛署藥輸字第020787號

產品資訊
有效成分之定性組成：Acarbose
有效成分之定量組成：
每錠Glucobay 50含acarbose 50毫克。
每錠Glucobay 100含acarbose 100毫克。
藥品外觀顏色：
50毫克錠劑：白色至淡黃色，圓形凸面錠劑，直徑7毫米，曲面半徑10毫米。錠劑的一面印有"G" and "50"，另一面有"Bayer cross"字樣。
100毫克錠劑：白色至淡黃色，圓形凸面錠劑，直徑9毫米，曲面半徑15毫米。錠劑的一面印有"G"，"score" and "50"，另一面有"Bayer cross"字樣。

適應症
非胰島素依賴型糖尿病之治療。

用法用量《本藥須由醫師處方使用》
一般建議劑量：
由於Glucobay的療效及耐受性因人而異，其劑量應由醫師作調整以適合每位病患。
劑量範圍
除非醫師另有指示，其建議劑量如下：
初期：一天三次，每次50毫克醣祿錠一錠 或 100毫克醣祿錠半錠。
後繼：一天三次，每次50毫克醣祿錠二錠 或 100毫克醣祿錠一錠。

有時需要最高劑量可一天三次200毫克的醣祿錠。
服藥4-8週後或病人在後繼治療後無法呈現適當的臨床反應，才能考慮增加劑量。病人雖嚴格遵守糖尿病飲食原則但有不適症狀發生，則不宜再增加劑量，必要時應酌予降低。平均劑量為日劑量醣祿錠 300毫克(相當於醣祿錠50毫克二錠每天三次或醣祿錠 100毫克一錠每天三次)。

預防葡萄糖耐受性不良*之患者成為第二型糖尿病患的用法用量：
*建議劑量*為每天三次100毫克的醣祿錠。
治療初期應給予一天一次50毫克的醣祿錠，然後在三個月內逐漸增加至一天三次100毫克的醣祿錠。
* 葡萄糖耐受性不良之定義：攝取葡萄糖之後2小時其血漿濃度在7.8~11.1 mmol/l (140~200mg/dl)間，且空腹血糖值在5.6~7.0 mmol/l (100~125mg/dl)間。

用藥方法
醣祿錠必須在用餐前，以少量液體，整顆吞服，或用餐時與前數口食物一起咬碎吞下。

老年人(65歲以上)：　並無建議此類病人須改變劑量或用藥頻率。
孩童：　見"警語及注意事項"。
肝功能不全病患：　在已有肝功能損害之病患無需調整劑量。
腎功能不全病患：　見"禁忌"。
治療期間：　並無預見醣祿錠的治療期長短需限制。

禁忌
對acarbose及或其賦形劑成分過敏者。
慢性腸胃道不適，伴隨明顯消化、吸收障礙者。
服用本劑，腸內氣體會增多，而惡化Roemheld's症、重度疝氣、腸阻塞、腸潰瘍者的病情。
醣祿錠不可使用於嚴重腎功能不全的病患(creatinine clearance < 25 ml/min)。

警語及注意事項
少數個案，可能發生無徵狀的肝酵素(liver enzyme)上升，因此在治療初期6-12個月應考慮適時測定肝酵素。經過評估，這些變化在停藥後可恢復正常。
本製劑對年齡18歲以下病患的藥效及耐受性尚未建立。

與其他藥物的交互作用以及其他型式的交互作用
使用醣祿錠的治療期間，食用蔗糖及含蔗糖食物時，由於結腸內碳水化合物的發酵作用增加，常引起腹部不適甚或腹瀉。
醣祿錠具有降血糖的作用但本身不會導致低血糖症。
醣祿錠和其他糖尿病治療劑如sulphonylurea、metformin或insulin合用而使血糖值降低到血糖過低範圍時，必須適量降低sulphonylurea、metformin或insulin的使用劑量。
個案可能發生低血糖休克。
如果急性低血糖症發生時，必須留意到服用醣祿錠會使蔗糖分解成果糖及葡萄糖的速度更緩慢，因此使用蔗糖並不適用於解除低血糖症，必須使用葡萄糖。
在個案中醣祿錠可能會影響到digoxin的生體可用率，而可能須調整digoxin劑量。
由於醣祿錠和cholestyramin、腸吸附劑(Intestinal absorbents)及消化酵素製劑(Digestal enzyme products)合用時，可能會影響醣祿錠的作用，必須避免同時服用。
並未觀察到與dimeticone/simeticone合用有交互作用產生。
醣祿錠和口服neomycin併用會加強飯後血糖的降低，增加胃腸副作用的頻率和嚴重性，如果症狀很嚴重，需考慮暫時減低醣祿錠的劑量。

懷孕與哺乳期
懷孕期
因尚無懷孕婦女服用本製劑的對照臨床試驗，懷孕婦女不可服用醣祿錠。
哺乳期
授乳老鼠，服用標的放射性acarbose後，發現有少量放射性存在乳汁中；在人類尚無同樣的發現，但仍不排除acarbose經由母乳對嬰兒之作用，原則上建議醫師不處方醣祿錠給哺乳婦女。

對駕駛及操作機械能力的影響
並無資料顯示Acarbose影響駕駛或操作機械的能力。

不良反應
以安慰劑做對照組的臨床試驗中所提到的藥品不良反應，依CIOMS III發生頻率表列如下 (在資料庫中的安慰劑對照臨床試驗：醣祿錠有8595位，安慰劑有7278位，至2006年2月10日為止)：

在每一發生頻率分組中，不良反應是依據嚴重程度遞減的方式呈現。
發生頻率定義：相當常見 (≥ 1/10)，常見 (≥ 1/100 to < 1/10)，不常見 (≥ 1/1,000 to < 1/100)，罕見 (≥ 1/10,000 to < 1/1,000)。
從上市後的調查報告所得到的不良反應 (至2005年12月31日為止)。不良反應的發生頻率無法估計時，則列在 "未知"欄。

系統器官分類： 臨床描述	相當常見 ≥ 10%	常見 ≥ 1% 至 < 10%	不常見 ≥ 0.1% 至 < 1%	罕見 ≥ 0.01% 至 < 0.1%	未知
血液及淋巴系統疾病					血小板減少
免疫系統疾病					過敏反應 (皮疹、紅斑、病疹、蕁麻疹)
血管疾病				水腫	
胃腸道疾病	胃腸脹氣	腹瀉、胃腸及腹部疼痛	噁心、嘔吐、消化不良		下腸阻塞/腸阻塞、腸氣囊病
肝膽疾病			肝臟酵素增加	黃膽	肝炎

"除了肝臟疾病，日本曾報導有肝功能不正常和肝損傷的案件"
在日本曾有發生猛爆性肝炎致死的個案，但是否與醣祿錠相關仍不清楚。
病患飲食不加節制，則有可能加重腸道的副作用。雖然遵守糖尿病飲食處方，但仍發生嚴重不適時，宜請教醫師，暫時或永久減低劑量。
病人每天服用建議劑量150-300毫克的醣祿錠，很少觀察到有臨床相關的不正常肝功能測試結果(超過正常值上限的三倍)。在服用醣祿錠進行治療時，不正常值可能是暫時的。(請同時參考警語及注意事項)。

服藥過量
當醣祿錠與含有碳水化合物 (雙醣，寡醣及多醣類) 的飲料或食物一起食用時，過量會造成脹氣、腹脹及腹瀉。
在不是與食物併用而醣祿錠過量的情形下，並不預期有過多的腸症狀出現。
過量的病人在四至六小時內，不可給予含有碳水化合物 (雙醣，寡醣及多醣類) 的飲食。

藥效學特性
醣祿錠的主成分為acarbose，是一種由微生物質萃取而得的偽四多醣(pseudotetrasaccharide)。
Acarbose主要在腸道發揮它的作用；其作用機轉主要是抑制腸道內負責分解雙醣、寡醣及多醣的酵素— α-glucosidase，而此種的作用機轉，可依據給藥劑量，延遲碳水化合物的分解。最重要的是，能延緩碳水化合物分解成葡萄糖進入全身循環。Acarbose藉由上述作用機轉，可延遲並減少飯後血糖升高，進而平衡經腸道對葡萄糖利用，而維持一天內平穩的血糖濃度，並且減少平均血糖值。
Acarbose降低了異常高濃度的糖化血紅蛋白。
在一個前瞻性、隨機、以安慰劑作對照的雙盲臨床試驗中(治療3~5年，平均治療時間為3.3年)，共有1429位葡萄糖耐受性不良*之受試者參與，其成為第二型糖尿病患之相對風險性降低25%。這些患者中，心血管疾病的發生率明顯地下降49%，而心肌梗塞的發生率明顯地下降91%。這些作用都在以acarbose治療第二型糖尿病的7個臨床試驗(共有2180位受試者，其中1248位服用acarbose、932位服用安慰劑)之回溯性統計分析(meta-analysis)中獲得證實：服用acarbose治療第二型糖尿病的患者，其發生心血管疾病的相對風險性降低35%，其罹患心肌梗塞的相對風險性降低64%，這兩個改變在統計學上是有意義的。
* 葡萄糖耐受性不良之定義：攝取葡萄糖之後2小時其血漿濃度在7.8~11.1 mmol/l (140~200mg/dl)間，且空腹血糖值在5.6~7.0 mmol/l (100~125mg/dl)間。

藥動學特性
以健康自願受試者口服經放射線標示的物質(200 mg)來研究acarbose的藥物動力學。
吸收
在96小時內，腎臟平均會將35%的總放射線活性(抑制性物質與其所有分解產物的總合)排出，因此假設吸收的程度至少在此範圍內。
血漿中的總放射線活性濃度變化過程有兩個高峰。第一個高峰出現在1.1 ± 0.3小時後，平均acarbose相等性濃度為52.2 ± 15.7 μg/l，這與該抑制性物質的濃度變化過程(2.1 ± 1.6小時後，49.5 ± 26.9 μg/l)的相關資料一致。第二個高峰出現在20.7 ± 5.2小時後，平均為586.3 ± 282.7 μg/l。與總放射線活性相比，此抑制性物質的最大血漿濃度低了10 – 20倍。大約14－24小時後出現的第二個高峰，被認為是來自於腸道較深部位細菌分解產物的吸收。
分佈
從健康受試者的血漿濃度變化過程計算得出的相對分佈體積(relative volume of distribution)為0.32 l/kg體重(靜脈注射，0.4 mg/kg體重)。
生體可用率(Bioavailability)：生體可用率只有1－2%。抑制性物質的全身性可用率如此低是合理的，因為acarbose的作用只侷限在腸道中。因此，生體可用率低與其療效無關。
排除
在分佈期(distribution phase)此抑制性物質的血漿清除半衰期為3.7 ± 2.7小時，在清除期(elimination phase)時則為9.6 ± 4.4小時。
從尿液排除的抑制性物質比例為使用劑量的1.7%。有51%的活性物質在96小時內從糞便中排除。

臨床前安全性資料
急性毒性
已經在小鼠、大鼠與狗進行口服及靜脈注射acarbose後的急性毒性研究。茲將急性毒性研究結果摘錄於下表。

種別	性別	給藥途徑		LD_{50}SIU/kg(1)	p < 0.05之信賴區間界限值
小鼠	雄性	口服	>	1000000	
小鼠	雄性	靜脈注射	>	500000	
大鼠	雄性	口服	>	1000000	
大鼠	雄性	靜脈注射		478000	(421000-546000)
大鼠	雌性	靜脈注射		359000	(286000-423000)
狗	雄性與雌性	口服	>	650000	
狗	雄性與雌性	靜脈注射	>	250000	

(1) 65000 SIU相當於約1 g的產品 (SIU＝蔗糖酶抑制單位 [saccharase inhibitory units])

根據這些結果，單一口服劑量後，acarbose可說是不具毒性；即使在使用10 g/kg的劑量之後，仍無法決定LD_{50} (半數致死量)。此外，在各個研究劑量範圍內，所有種別試驗動物都未觀察到中毒症狀。
以靜脈注射後，此物質也幾乎不具毒性。

亞慢性毒性 (Subchronic toxicity)
已於大鼠與狗進行過為期3個月的耐受性研究。在大鼠中，研究的acarbose劑量為口服50-450 mg/kg。相較於未接受acarbose的對照組，所有血液學與臨床化學參數都維持不變。隨後的組織病理學研究在各個劑量同樣都看不到任何組織破壞的證據。
狗的研究劑量為口服50-450 mg/kg。相較於未接受acarbose的對照組，受測物質引起的變化會顯現在動物的體重發展、血清中α-澱粉酶 (α-amylase)的活性以及血尿濃度，所有劑量組的體重發展都受到影響。如果每天固定給予350 g的飼料，在研究前4週，組平均值會明顯下降。當研究第5週將飼料量增加為一天500 g時，動物的體重就可以維持在一定。超過治療劑量之acarbose所引發的體重變化，應視為是受測試物質因等熱能(isocaloric)飼料失衡(失去碳水化合物)而導致藥效學活性增加之表現，不代表真正的毒性作用。尿素濃度稍增也應視為治療的間接結果，亦即是隨體重下降所伴隨的分解性(catabolic)代謝狀況。α-澱粉酶活性下降也可解讀為藥效作用增加的跡象。

慢性毒性
已在大鼠、狗與倉鼠進行治療期分別為24個月、12個月與80週的慢性研究。除了長期用藥可能帶來的損壞問題外，大鼠與倉鼠研究也有意探討可能的致癌作用。

致癌性
已有許多探討致癌性的研究。
在Sprague-Dawley大鼠的飼料中添加acarbose(最高4500 ppm)長達24－26個月。添加acarbose的飼料中會引起動物相當嚴重的營養失調。相較於對照組，腎臟實質組織(parenchyma)腫瘤(腺瘤[adenoma]、腎上腺樣癌[hypernephroid carcinoma])的形成與劑量有關，然而整體腫瘤發生率(尤其是荷爾蒙相關腫瘤之發生率)降低。
為了防止營養失調，後續的研究都會額外給予動物葡萄糖替代物。在劑量為4500 ppm acarbose及外加葡萄糖替代物時，其體重比對照組少了10%。未發現腎臟腫瘤發生率增加之情況。
在無外加葡萄糖替代物之下重複此研究(為期26個月)時發現，睪丸萊狄氏細胞(Leydig cells)的良性腫瘤增加。所有接受外加葡萄糖替代物的組別，血中葡萄糖濃度都有(有時為病理性)上升(使用大量葡萄糖所引起的營養性糖尿病)。
經由胃管給予acarbose時，體重會維持在控制範圍內，而此研究設計避免藥效活性(pharmacodynamic activity)升高。腫瘤發生率則正常。
Wistar大鼠經由飼料或胃管給予0-4500 ppm acarbose持續30個月。經由飼料給予acarbose未導致體重明顯下降。添加500 ppm acarbose會使盲腸變大。整體腫瘤發生率下降；沒有腫瘤發生率增加的證據。
在倉鼠的飼料中添加0-4000 ppm acarbose的研究持續80週，有或無外加葡萄糖替代物。在最高劑量組的動物中可觀察到血中葡萄糖濃度升高。腫瘤發生率則未提高。

生育毒性
在大鼠與兔子進行致畸胎作用的研究中，使用的劑量為口服0、30、120與480 mg/kg。在大鼠的研究中，治療時間從懷孕的第6天到第15天；在兔子的研究中，則從懷孕的第6天到第18天。
在測試的劑量範圍內，兩種動物都未發現acarbose引起致畸胎作用的證據。
雄性或雌性大鼠接受最高每天540 mg/kg劑量時，並未發現生育力受損的情形。
大鼠在胎兒發育與泌乳期間接受每天540 mg/kg的劑量，對生產過程或幼鼠並無影響。目前尚無在人類懷孕與泌乳期間使用acarbose的資料。

致突變性
許多致突變性研究結果尚未發現acarbose任何基因毒性作用的證據。

藥劑特性
賦形劑
Microcrystalline cellulose;
Silicia, colloidal anhydrous;
Magnesium stearate;
Maize starch

儲存注意事項
貯存溫度不得超過30℃。藥品必須置於兒童無法觸及之處。
若在溫度25℃及相對濕度60%以下儲存，取出的錠劑可至多保存2星期。若在更高的溫度且/或更高的相對濕度，未儲存在原包裝的錠劑會有變色的情形，因此，直到要使用前才將錠劑自瓶子或鋁箔片中取出。

包裝
6-1000錠瓶裝及盒裝。

製造廠：Bayer Schering Pharma AG
廠　址：D-51368 Leverkusen, Germany
藥　商：台灣拜耳股份有限公司
地　址：台北市信義路五段7號54樓
電　話：(02)81011000
網　址：www.bayerscheringpharma.com.tw
Glucobay Tablets 50mg, 100mg / CCDS19 / TW09 / 032010

Glucobay® Tablets 50mg, 100mg

α-Glucosidase inhibitor

Tablets for oral administration

GENERAL INFORMATION
Qualitative composition in terms of the active ingredient:
Acarbose
Quantitative composition in terms of the active ingredient(s) per dosage form:
Glucobay 50 mg tablets: 1 tablet contains 50 mg acarbose
Glucobay 100 mg tablets: 1 tablet contains 100 mg acarbose
Appearance colour of the drug product:
Tablets 50 mg: White to yellow-tinged round, convex tablets of 7 mm diameter and 10 mm radius of curvature. On one side the tablet code is “G” and “50” and on the other side “Bayer cross”.
Tablets 100 mg: White to yellow-tinged round, convex tablets of 9 mm diameter and 15 mm radius of curvature. On one side the tablet code is “G”, “score” and “100” and on the other side “Bayer cross”.

INDICATIONS
Additional therapy in association with diet in patients with diabetes mellitus.

POSOLOGY AND METHOD OF ADMINISTRATION
Recommended usual dose:
The dosage must be adjusted by the doctor to suit each patient, because efficacy and tolerability vary from one individual to another.
Dosage regimen:
Unless otherwise prescribed the recommended dosage is as follows:

Initially	3 x 1 tablet of	50 mg Glucobay/day or	3 x ½ tablet of	100 mg Glucobay /day
up to	3 x 2 tablets of	50 mg Glucobay/day or	3 x 1 tablet of	100 mg Glucobay day

A further increase in dosage to 3 x 200 mg Glucobay/day may occasionally be necessary.
The dose may be increased after 4 – 8 weeks, and if patients show an inadequate clinical response in the later course of the treatment. If distressing complaints develop in spite of strict adherence to the diet, the dose should not be increased further, and if necessary should be somewhat reduced. The average dose is 300 mg Glucobay / day (corresponding to 3 x 2 tablets of Glucobay tablets 50 mg/day, or 3 x 1 tablet of Glucobay tablets 100 mg/day).
Recommended usual dose for the prevention of type 2 diabetes in patients with impaired glucose tolerance*:
Recommended dose: 3 x 100 mg Glucobay /day
Treatment should be initiated with a dose of 50 mg OD and escalated to 3 x 100 mg/day within 3 months.
*defined as 2 hour post-glucose load plasma concentrations (2HPG) between 7.8 and 11.1 mmol/l (140–200 mg/dl) and fasting values between 5.6 and 7.0 mmol/l (100-125 mg/dl)
Method of administration:
Glucobay tablets are effective only if swallowed whole with a little liquid directly before the meal or be chewed with the first few mouthfuls of the meal.
Elderly (above 65 years):
No alteration of dosage or dosing frequency is recommended with regard to the age of the patients.
Children:
(see Special Warnings and Precautions for Use)
Hepatic impairment:
No dose adjustment is required in patients with pre-existing impaired hepatic function.
Renal impairment:
(see Contraindications)
Duration of use:
It is not envisaged that there will be any time restriction in the use of Glucobay tablets.

CONTRAINDICATIONS
Hypersensitivity to acarbose and/or to inactive constituents.
Chronic intestinal disorders associated with distinct disturbances of digestion and absorption.
States which may deteriorate as a result of increased gas formation in the intestine (e.g. Roemheld's syndrome, major hernias, intestinal obstructions, and intestinal ulcers).
Glucobay is contraindicated in patients with severe renal impairment (creatinine clearance < 25ml/min).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Asymptomatic liver enzyme elevations may occur in individual cases. Therefore liver enzyme monitoring should be considered during the first 6 to 12 months of treatment. In evaluable cases these changes were reversible on discontinuation of Glucobay therapy.
Safety and efficacy of Glucobay in patients under 18 years of age have not been established.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Sucrose (cane sugar) and foods containing sucrose often cause abdominal discomfort or even diarrhoea during treatment with Glucobay tablets as a result of increased carbohydrate fermentation in the colon.
Acarbose has an antihyperglycaemic effect, but does not itself induce hypoglycaemia.
If Glucobay tablets are prescribed in addition to drugs containing sulphonylureas or metformin, or in addition to insulin, a fall of the blood glucose values into the hypoglycaemic range may necessitate a suitable decrease in the sulphonylurea, metformin or insulin dose. In individual cases hypoglycaemic shock may occur.
If acute hypoglycaemia develops it should be borne in mind that sucrose (cane sugar) is broken down into fructose and glucose more slowly during treatment with Glucobay; for this reason sucrose is unsuitable for a rapid alleviation of hypoglycaemia and glucose should be used instead.
In individual cases Glucobay may affect digoxin bioavailability, which may require dose adjustment of digoxin.
Because they may possibly influence the action of Glucobay tablets, simultaneous administration of cholestyramine, intestinal adsorbents and digestive enzyme products should be avoided.
The concomitant administration of Glucobay and oral neomycin may lead to enhanced reductions of postprandial blood glucose and to an increase in the frequency and severity of gastro-intestinal side-effects. If the symptoms are severe, a temporary dose reduction of Glucobay may be considered.

PREGNANCY AND LACTATION
Pregnancy
Glucobay should not be administered during pregnancy, as no information from controlled clinical studies is available on its use in pregnant women.
Lactation
After administration of radiolabelled acarbose to lactating rats a small quantity of the radioactivity was found in the milk. There are as yet no corresponding findings in humans. However, as drug induced effects of acarbose in milk have not been excluded in babies, in principle it is advisable not to prescribe acarbose during the breastfeeding period.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No data on impaired ability to drive and operate machinery are available for acarbose.

UNDESIRABLE EFFECTS
The frequencies of Adverse drug reactions (ADRs) based on placebo-controlled studies with Glucobay sorted by CIOMS III categories of frequency (placebo-controlled studies in clinical trial database: Glucobay N = 8,595; placebo N = 7,278; status: 10 Feb 2006) are summarized in the table below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).
The ADRs identified only during postmarketing surveillance (status:31 Dec 2005), and for which a frequency could not be estimated, are listed under “not known”.

Clinical Description	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%	Unknown
Blood and lymphatic system disorders					**Thrombocytopenia**
Immune system disorders					**Allergic reaction (rash, erythema, exanthema, urticaria)**
Vascular disorders				**Oedema**	
Gastro-intestinal disorders	**Flatulence**	**Diarrhea Gastrointestinal and abdominal pains**	**Nausea Vomiting Dyspepsia**		**Subileus/Ileus Pneumatosis cystoidis intestinalis**
Hepatobiliary disorders			**Increase in liver enzymes**	**Jaundice**	**Hepatitis**

“In additional events reported as liver disorder, hepatic function abnormal, and liver injury have been received especially from Japan.”

Individual cases of fulminant hepatitis with fatal outcome have been reported in Japan. The relationship to Glucobay is unclear.
If the prescribed diabetic diet is not observed the intestinal side effects may be intensified.
If strongly distressing symptoms develop in spite of adherence to the diabetic diet prescribed, the doctor must be consulted and the dose temporarily or permanently reduced.
In patients receiving the recommended daily dose of 150 to 300 mg Glucobay/day, rarely clinically relevant abnormal liver function tests (three times above upper limit of normal range) were observed. Abnormal values may be transient under ongoing Glucobay therapy (see “Special Warnings and Precautions for Use”).

OVERDOSE
When Glucobay tablets are taken with drinks and/or meals containing carbohydrates (polysaccharides, oligosaccharides, or disaccharides), overdosage can lead to meteorism, flatulence, and diarrhoea.
In the event of Glucobay tablets being taken in an overdose independently of food, excessive intestinal symptoms need not be anticipated.
In cases of overdosage the patient should not be given drinks or meals containing carbohydrates (polysaccharides, oligosaccharides, and disaccharides) for the next 4-6 h.

PHARMACODYNAMIC PROPERTIES
The active ingredient of acarbose tablets is acarbose, a pseudotetrasaccharide of microbial origin.
In all species tested acarbose exerts its activity in the intestinal tract. The action of acarbose is based on inhibition of the intestinal enzymes (α-glucosidases) involved in the degradation of disaccharides, oligosaccharides, and polysaccharides.
This leads to a dose-dependent delay in the digestion of these carbohydrates.
Most importantly, glucose derived from carbohydrates is released and taken up into the blood more slowly. In this way acarbose postpones and reduces the post-prandial rise in blood glucose. As a result of the balancing effect on the uptake of glucose from the intestine, the blood glucose fluctuations over the day are reduced and the mean blood glucose values decrease.
Acarbose lowers abnormally high concentrations of glycosylated haemoglobin.
In a prospective, randomized, placebo-controlled, double-blind study (treatment 3-5 years, average 3,3 years) with 1429 subjects with confirmed impaired glucose tolerance* the relative risk of developing type 2 diabetes was reduced by 25%. In these patients the incidence of all cardiovascular events decreased significantly by 49%, while the incidence of MI was significantly reduced by 91%.
These effects were confirmed by a retrospective meta-analysis of 7 placebo controlled trials (total of 2180 patients, 1248 Acarbose, 932 placebos) of Acarbose in the treatment of type 2 diabetes. In these patients the relative risk of any cardiovascular event was reduced by 35%, while the relative risk of myocardial infarction was decreased by 64%. Both changes were statistically significant.
*defined as 2 hour post-glucose load plasma concentrations (2HPG) between 7.8 and 11.1 mmol/l (140-200 mg/dl) and fasting values between 5.6 and 7.0 mmol/l (100-125 mg/dl)

PHARMACOKINETIC PROPERTIES
The pharmacokinetics of acarbose was investigated after oral administration of the labelled substance (200 mg) to healthy volunteers.
Absorption
Since on average 35% of the total radioactivity (sum of the inhibitory substance and any degradation products) was excreted by the kidneys within 96 hours, it can be assumed that the degree of absorption is at least in this range.
The course of the total radioactivity concentration in plasma went through two peaks. The first peak, with an average acarbose-equivalent concentration of 52.2 ± 15.7 µg/L after 1.1 ± 0.3 hours, is in agreement with corresponding data for the concentration course of the inhibitor substance (49.5 ± 26.9 µg/L after 2.1 ± 1.6 hours). The second peak is on average 586.3 ± 282.7 µg/L and is reached after 20.7 ± 5.2 hours. In contrast to the total radioactivity, the maximum plasma concentrations of the inhibitory substance are lower by a factor of 10 - 20. The second, higher peak after about 14 - 24 hours is believed to be due to absorption of bacterial degradation products from deeper parts of the intestine.
Distribution
A relative volume of distribution of 0.32 L/kg body weight has been calculated in healthy volunteers from the concentration course in the plasma (intravenous dosing, 0.4 mg/kg b.w.).
Bioavailability: The bioavailability is 1 - 2% only. This extremely low systemically available percentage of inhibitory substance is desirable, because acarbose acts only locally in the intestine. Thus, this low Bioavailability has no relevance for the therapeutic effect.
Excretion
The plasma elimination half-lives of the inhibitory substance are 3.7 ± 2.7 hours for the distribution phase and 9.6 ± 4.4 hours for the elimination phase.
The proportion of inhibitory substance excreted in the urine was 1.7% of the administered dose. 51% of the activity was eliminated within 96 hours in the faeces.

PRECLINICAL SAFETY DATA
Acute toxicity:
Acute toxicity studies after oral and intravenous administration of acarbose have been conducted in mice, rats and dogs. The results of the acute toxicity studies are summarized in the table below.

Species	Sex	Route of Administration		LD_{50}SIU/kg(3)	Confidence limits for p<0.05
Mouse	m(1)	per os	>	1000000	
Mouse	m	i.v.	>	500000	
Rat	m	per os	>	1000000	
Rat	m	i.v.		478000	(421000-546000)
Rat	f(2)	i.v.		359000	(286000-423000)
Dog	m and f	per os	>	650000	
Dog	m and f	i.v.	>	250000	

(1) Male
(2) Female
(3) 65000 SIU correspond to about 1 g of the product
(SIU = saccharase inhibitory units)

On the basis of these results acarbose may be described as non toxic after single oral doses; even after doses of 10 g/kg an LD_{50} could not be determined. Moreover, no symptoms of intoxication were observed in any of the test species in the dose range under investigation.
The substance is also practically non toxic after i.v. administration.

Subchronic toxicity:
Tolerability studies have been conducted in rats and in dogs over periods of 3 months. In rats acarbose has been investigated in doses of 50-450 mg/kg p.o. All haematological and clinicochemical parameters remained unchanged compared to a control group receiving no acarbose. Subsequent histo-pathological investigations similarly yielded no evidence of damage at any dose.
Doses of 50-450 mg/kg p.o. have also been investigated in dogs. Compared to a control group which received no acarbose, changes due to the test substance were demonstrated in the development of the animals' body weight, α-amylase activity in the serum, and the blood urea concentration. In all dose groups the body weight development was influenced in that when constant quantity of 350 g feed/day had been given the mean group values fell distinctly during the first 4 weeks of the study. When the quantity of feed provided had been increased to 500 g/day in the 5th week of the study, the animals remained at the same weight level. These weight changes induced by acarbose in quantities exceeding the therapeutic dose should be regarded as an expression of increased pharmacodynamic activity of the test substance due to an isocaloric feed imbalance (loss of carbohydrates); they do not represent an actual toxic effect. The slight increases in the urea concentration should also be regarded as an indirect result of the treatment, i.e. of a catabolic metabolic situation developing with the loss in weight. The diminished α-amylase activity can also be interpreted as a sign of increased pharmacodynamic effect.
Chronic toxicity:
Chronic studies have been conducted in rats, dogs, and hamsters, with treatment durations of respectively 24 months, 12 months, and 80 weeks. In addition to the question of damage caused by chronic administration, the studies in rats and hamsters were also intended to address possible carcinogenic effects.
Carcinogenicity:
A number of studies are available on carcinogenicity.
Sprague-Dawley rats received up to 4500 ppm acarbose in feed over a period of 24-26 months. Administration of acarbose in the feed caused considerable malnutrition in the animals. Under these study conditions, tumours of the renal parenchyma (adenoma, hypernephroid carcinoma) were found dose-dependently compared to the controls, while the overall tumour rate (in particular the rate for hormone dependent tumours) decreased.

To prevent malnutrition, in subsequent studies the animals received glucose substitution. At a dose of 4500 ppm acarbose plus glucose substitution, the body weight was 10% lower than in the control group. An increased incidence of renal tumours was not observed.
When the study was repeated without glucose substitution over a 26-month period, an increase in benign tumours of Leydig cells of the testes was also observed. In all groups receiving glucose substitution the glucose values were (sometimes pathologically) elevated (alimentary diabetes on administration of large quantities of glucose).
On administration of acarbose via a stomach tube the body weights were within the control range, and with this study design elevated pharmacodynamic activity was avoided. The tumour rate was normal.
Wistar rats received 0-4500 ppm acarbose for 30 months in feed or via a stomach tube. Administration of acarbose in the feed did not lead to any pronounced weight loss. From 500 ppm acarbose the caecum was enlarged. The overall tumour rate decreased, and there was no evidence of an increased incidence of tumours.
Hamsters received 0-4000 ppm acarbose in feed over 80 weeks, with and without glucose substitution. Increased blood glucose concentrations were seen in animals of the highest-dose group. Tumour incidences were not elevated
Reproduction toxicology:
Investigations for teratogenic effects were conducted in rats and in rabbits, using doses of 0, 30, 120, and 480 mg/kg p.o. in both species. In the rats the treatment was administered from the 6th to the 15th day of gestation, and in the rabbits from the 6th to the 18th day of gestation.
There was no evidence of teratogenic effects due to acarbose in either species in the range of doses under test.
No impairment of fertility was observed in male or female rats up to a dose of 540 mg/kg/day.
Administration of up to 540 mg/kg/day during foetal development and lactation in rats had no effect on the birth process or the young. No data are available on the use of acarbose during pregnancy and lactation in humans.
Mutagenicity:
According to a number of mutagenicity studies, there is no evidence of any genotoxic action of acarbose.

PHARMACEUTICAL PARTICULARS
List of excipients:
Microcrystalline cellulose;
Silicia, colloidal anhydrous;
Magnesium stearate;
Maize starch
Special precautions for storage:
Do not store above 30°C. Keep drugs out of reach of children.
Instructions for use / handling:
At storage conditions up to 25°C and below 60 % relative humidity the unpacked tablets can be stored for up to two weeks. At higher temperatures and/or higher relative humidity, discoloration can occur in tablets that are not in the pack. The tablets should therefore only be removed from the foil or bottle immediately prior to use

Presentation
6 -1000’s per bottle or box.

Bayer Schering Pharma AG, D-51368 Leverkusen, Germany
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